

Exhibit C

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EXHIBIT 21

2011 REMS for NDA 20-687 Mifeprex

NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg

Danco Laboratories, LLC

PO Box 4816

New York, NY 10185

I. GOALS

- A. To provide information to patients about the benefits and risks of MIFEPREX before they make a decision whether to take the drug.
- B. To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe MIFEPREX and are able to assure patient access to appropriate medical facilities to manage any complications.

II. REMS ELEMENTS

A. Medication Guide

- 1. A Medication Guide will be dispensed with each MIFEPREX prescription in accordance with 21 CFR 208.24.
- 2. Please see the appended Medication Guide.

B. Elements to Assure Safe Use

- 1. Healthcare providers who prescribe MIFEPREX will be specially certified.

Danco will ensure that healthcare providers who prescribe MIFEPREX are specially certified.

- a. To become specially certified, each prescriber must complete and fax to the MIFEPREX distributor the one-time Prescriber's Agreement, agreeing that they meet the qualifications and will follow the guidelines outlined in the Prescriber's Agreement.
- b. The following materials are part of the REMS and are appended:
 - i. Prescriber's Agreement.
 - ii. Patient Agreement.

2. MIFEPREX will be dispensed only in certain health care settings, specifically clinics, medical offices, and hospitals.

Danco will ensure that MIFEPREX will only be available to be dispensed in a clinic, medical office, or hospital, by or under the supervision of a specially certified prescriber. MIFEPREX will not be distributed to or dispensed through retail pharmacies.

3. MIFEPREX will only be dispensed to patients with documentation of safe use conditions.

Danco will ensure that MIFEPREX will only be dispensed to patients with documentation of the following safe use conditions:

- a. The patient has completed and signed the Patient Agreement, and the Patient Agreement has been placed in the patient's medical record.
- b. The patient has been provided copies of the signed Patient Agreement and the Medication Guide.

C. Implementation System

The Implementation System will include the following:

1. Distributors who distribute MIFEPREX will be certified. To become certified, distributors must agree to:
 - a. Ship drug only to site locations identified by specially certified prescribers in signed Prescriber's Agreements, and maintain secure and confidential records of shipments.
 - b. Follow all distribution guidelines, including those for storage, tracking package serial numbers, proof of delivery, and controlled returns.
2. Danco will assess the performance of the certified distributors with regard to the following:
 - a. Whether a secure, confidential and controlled distribution system is being maintained with regard to storage, handling, shipping, and return of MIFEPREX.
 - b. Whether MIFEPREX is being shipped only to site locations identified by specially certified prescribers in the signed Prescriber's Agreement and only available to be dispensed to patients in a clinic, medical office, or hospital by or under the supervision of a specially certified prescriber.

3. If Danco determines the distributors are not complying with these requirements, Danco will take steps to improve their compliance.

D. Timetable for Submission of Assessments

Danco will submit REMS assessments to the FDA one year from the date of the approval of the REMS and every three years thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the assessment reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Danco will submit each assessment so that it will be received by the FDA on or before the due date.

MEDICATION GUIDE

Mifeprex[®] (MIF-eh-prex)
(mifepristone)

Read this information carefully before taking Mifeprex* and misoprostol. It will help you understand how the treatment works. This MEDICATION GUIDE does not take the place of talking with your health care provider (provider).

What is Mifeprex?

Mifeprex is used to end an early pregnancy. It blocks a hormone needed for your pregnancy to continue. It is not approved for ending later pregnancies. Early pregnancy means it is 49 days (7 weeks) or less since your last menstrual period began. When you use Mifeprex (Day 1), you also need to take another medicine misoprostol, 2 days after you take Mifeprex (Day 3), to end your pregnancy. But, about 5-8 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Prompt medical attention is needed in these circumstances. Serious infection has resulted in death in a very small number of cases; in most of these cases misoprostol was used in the vagina. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your provider. Your provider's telephone number is _____.

Be sure to contact your provider promptly if you have any of the following:

Heavy Bleeding. Contact your provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical abortion/D&C) to stop it.

Abdominal Pain or "Feeling Sick". If you have abdominal pain or discomfort, or you are "feeling sick", including weakness, nausea, vomiting or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

Fever. In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your provider right away. Fever may be a symptom of a serious infection or another problem (including an ectopic pregnancy).

Take this MEDICATION GUIDE with you. When you visit an emergency room or a provider who did not give you your Mifeprex, you should give them your MEDICATION GUIDE so that

they understand that you are having a medical abortion with Mifeprex.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy. There is a chance that there may be birth defects if the pregnancy is not ended.

Talk with your provider. Before you take Mifeprex, you should read this MEDICATION GUIDE and sign a statement (PATIENT AGREEMENT). You and your provider should discuss the benefits and risks of your using Mifeprex.

Who should not take Mifeprex?

Some women should not take Mifeprex. Do not take it if:

- It has been more than 49 days (7 weeks) since your last menstrual period began.
- You have an IUD. It must be taken out before you take Mifeprex.
- Your provider has told you that you have a pregnancy outside the uterus (ectopic pregnancy).
- You have problems with your adrenal glands (chronic adrenal failure).
- You take a medicine to thin your blood.
- You have a bleeding problem.
- You take certain steroid medicines.
- You cannot return for the next 2 visits.
- You cannot easily get emergency medical help in the 2 weeks after you take Mifeprex.
- You are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Tell your provider about all your medical conditions to find out if you can take Mifeprex. Also, tell your provider if you smoke at least 10 cigarettes a day.

How should I take Mifeprex?

- **Day 1 at your provider's office:**
 - Read this MEDICATION GUIDE.
 - Discuss the benefits and risks of using Mifeprex to end your pregnancy.
 - If you decide Mifeprex is right for you, sign the PATIENT AGREEMENT.
 - After getting a physical exam, swallow 3 tablets of Mifeprex.
- **Day 3 at your provider's office:**
 - If you are still pregnant, take 2 misoprostol tablets.
 - Misoprostol may cause cramps, nausea, diarrhea, and other symptoms. Your provider may send you home with medicines for these symptoms.
- **About Day 14 at your provider's office:**
 - This follow-up visit is very important. You must return to the provider about 14 days after you have taken Mifeprex to be sure you are well and that you are not pregnant.
 - Your provider will check whether your pregnancy has completely ended. If it has not ended, there is a chance that there may be birth defects. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or non-prescription medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your provider about them because they may interfere with the treatment. Ask your provider about what medicines you can take for pain.

If you are breastfeeding at the time you take Mifeprex and misoprostol, discuss with your provider if you should stop breastfeeding for a few days.

What are the possible and reasonably likely side effects of Mifeprex?

Cramping and bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must return to your provider on Day 3 and about Day 14. See “How should I take Mifeprex?” for more information on when to return to your provider. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take on Day 3. Bleeding or spotting can be expected for an average of 9–16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of ending the pregnancy.

Other common symptoms of treatment include diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness. These side effects lessen after Day 3 and are usually gone by Day 14. Your provider will tell you how to manage any pain or other side effects.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

* * *

Medicines are sometimes prescribed for purposes other than those listed in a MEDICATION GUIDE. For more information, ask your provider for the information about Mifeprex that is written for health care professionals. Ask your provider if you have any questions.

This MEDICATION GUIDE has been approved by the U.S. Food and Drug Administration.

Rev 3: 4/22/09

*Mifeprex is a registered trademark of Danco Laboratories, LLC.

M I F E P R E X[®]
(Mifepristone) Tablets, 200 mg

PRESCRIBER'S AGREEMENT

We are pleased that you wish to become a provider of Mifeprex* (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.
- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.
- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.
- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this identification number in each patient's record.

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com
*MIFEPREX is a registered trademark of Danco Laboratories, LLC.

ACCOUNT SETUP FORM**MIFEPREX™ (Mifepristone) Tablets, 200 mg; NDC 64875-001-03**

To set up your
account:

1

Read the Prescriber's Agreement on
the back of this Account Setup Form.

2

Complete and sign this form.

3

Fax the completed Account Setup
Form to the Danco distributor at
1-866-227-3343. Your account
information will be kept strictly
confidential.

4

The distributor will call to finalize
your account setup and take your
initial order.

5

Subsequent orders may be phoned
in and are usually shipped within
24 hours.

6

Unopened, unused product may be
returned for a refund or exchange up
to a year after the expiration date.

Billing information

Bill to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

Shipping information (☐ Check if same as above)

Ship to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

Additional site locations

I will also be prescribing Mifeprex* at these additional locations:

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

(Any additional sites may be listed on an attached sheet of paper.)

Request additional materials☐ Medication Guides ☐ Patient Agreements☐ State Abortion Guidelines ☐ Patient Brochures**Establishing your account (required only with first order)**

Each facility purchasing Mifeprex must be included on this form (see additional site locations box above) before the distributor can ship the product. Please read the Prescriber's Agreement on the reverse of this form and sign below.

By signing below, you acknowledge receipt of the Prescriber's Agreement and agree that you meet these qualifications and that you will follow these guidelines for use.

Print Name _____ Signature _____

Medical License # _____ Date _____

Fax this completed Account Setup Form to the authorized distributor. Fax: 1-866-227-3343

Please fax any questions to the above number or call 1-800-848-6142.

*Mifeprex is a trademark of Danco Laboratories, LLC.



Mifeprex® (Mifepristone) Tablets, 200 mg

PATIENT AGREEMENT

Mifeprex* (mifepristone) Tablets

1. I have read the attached MEDICATION GUIDE for using Mifeprex and misoprostol to end my pregnancy.
2. I discussed the information with my health care provider (provider).
3. My provider answered all my questions and told me about the risks and benefits of using Mifeprex and misoprostol to end my pregnancy.
4. I believe I am no more than 49 days (7 weeks) pregnant.
5. I understand that I will take Mifeprex in my provider's office (Day 1).
6. I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3).
7. My provider gave me advice on what to do if I develop heavy bleeding or need emergency care due to the treatment.
8. Bleeding and cramping do not mean that my pregnancy has ended. Therefore, I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
9. I know that, in some cases, the treatment will not work. This happens in about 5 to 8 women out of 100 who use this treatment.
10. I understand that if my pregnancy continues after any part of the treatment, there is a chance that there may be birth defects. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about my choices, which may include a surgical procedure to end my pregnancy.
11. I understand that if the medicines I take do not end my pregnancy and I decide to have a surgical procedure to end my pregnancy, or if I need a surgical procedure to stop bleeding, my provider will do the procedure or refer me to another provider who will. I have that provider's name, address and phone number.
12. I have my provider's name, address and phone number and know that I can call if I have any questions or concerns.
13. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
14. I will do the following:
 - contact my provider right away if in the days after treatment I have a fever of 100.4°F or higher that lasts for more than 4 hours or severe abdominal pain.
 - contact my provider right away if I have heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours).
 - contact my provider right away if I have abdominal pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting or diarrhea, more than 24 hours after taking misoprostol.
 - take the MEDICATION GUIDE with me when I visit an emergency room or a provider who did not give me Mifeprex, so that they will understand that I am having a medical abortion with Mifeprex.
 - return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.
 - return to my provider's office about 14 days after beginning treatment to be sure that my pregnancy has ended and that I am well.

Patient Signature: _____

Patient Name (print): _____

Date: _____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for mifepristone.

Provider's Signature: _____

Name of Provider (print): _____

Date: _____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record. Give a copy of the MEDICATION GUIDE to the patient.

Rev 2: 7/19/05

*Mifeprex is a registered trademark of Danco Laboratories, LLC.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

06/08/2011

EXHIBIT 22

FDA Letter to AAPLOG Denying 2002 Citizens Petition (March 29, 2016)



DEPARTMENT OF HEALTH & HUMAN SERVICES

MAR 29 2016

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

Donna Harrison, M.D.
Executive Director
American Association of Pro Life Obstetricians and Gynecologists
P.O. Box 395
Eau Claire, MI 49111

Gene Rudd, M.D.
Senior Vice President
Christian Medical and Dental Associations
P.O. Box 7500
Bristol, TN 37621

Penny Young Nance
CEO and President
Concerned Women for America
1015 Fifteenth St., NW
Suite 1100
Washington, DC 20005

Re: Docket No. FDA-2002-P-0364

Dear Drs. Harrison and Rudd and Ms. Nance:

This letter responds to your citizen petition submitted on August 20, 2002, to the Food and Drug Administration (FDA or Agency) on behalf of the American Association of Pro Life Obstetricians and Gynecologists (AAPLOG), the Christian Medical Association (CMA) (n/k/a the Christian Medical and Dental Associations), and Concerned Women for America (CWA) (Petition).¹ Your Petition requests that the Agency stay FDA's approval of Mifeprex (mifepristone, also known as RU-486), thereby halting the distribution and marketing of the drug pending final action on the Petition. The Petition also requests that the Agency revoke FDA's approval of Mifeprex and requests a full audit of the French and U.S. clinical trials submitted in support of the new drug application (NDA) for Mifeprex.

We have carefully considered the information submitted in your Petition, comments on your Petition submitted to the docket, other submissions to the docket, and other relevant data available to the Agency. Based on our review of these materials and for the reasons described below, your Petition is denied.

¹ The citizen petition was originally assigned docket number 2002P-0377/CP1. The number was changed to FDA-2002-P-0364 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008. This citizen petition was submitted by AAPLOG, CMA, and Sandy Rios, the then-President of CWA. We have addressed this response to CWA's current CEO and President, Penny Young Nance.

I. BACKGROUND

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (NDA 20-687). The application was approved under 21 CFR part 314, subpart H, "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the approval letter, including a requirement that Mifeprex be provided by or under the supervision of a physician who meets eight qualifications specified in the letter.

The September 28, 2000, approval letter also listed two Phase 4 commitments² that the then-applicant of the Mifeprex NDA (i.e., the Population Council)³ agreed to meet. In addition, the letter stated that FDA was waiving the pediatric study requirement in 21 CFR 314.55.

II. DISCUSSION OF ISSUES RAISED

You maintain that good cause exists for granting an immediate stay of the Mifeprex approval and for the subsequent revocation of that approval under 21 CFR 314.530 (Petition at 3). You contend that:

- The approval of Mifeprex in 2000 violated the Administrative Procedure Act's (APA's) prohibition against agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law (5 U.S.C. 706(2)(A));
- The 2000 approval violated section 505 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355) because Mifeprex does not satisfy the safety and labeling requirements of that section; and
- FDA approved Mifeprex in 2000 despite the presence of substantial risks to women's health, including fatal hemorrhage and serious bacterial infections.

You make eight arguments for the stay and revocation of the 2000 Mifeprex approval, as follows (Petition at 4-7):

² For purposes of this petition response, the term 'Phase 4 commitments' refers to the postmarketing studies that the Mifeprex sponsor agreed to perform as a condition of approval.

³ Effective October 31, 2002, the Population Council transferred ownership of the Mifeprex NDA to Danco Laboratories, LLC (Danco), which had been licensed to manufacture and market Mifeprex.

- That the approval of Mifeprex in 2000 violated the legal requirements of the accelerated approval regulations under 21 CFR Subpart H.
- That Mifeprex was not proven safe and effective in 2000 as required by law.
- That the Mifeprex regimen requires that Mifeprex be used in conjunction with another drug, misoprostol, which has not been separately approved as an abortifacient.
- That the Mifeprex regimen was approved in 2000 without adequate safety restrictions.
- That the drug's sponsor, following the approval in 2000, neglected to require Mifeprex providers to adhere to the restrictions contained in the regimen approved at that time.
- That the safeguards employed in one of the clinical trials that supported the 2000 approval were not mirrored in the regimen that FDA approved.
- That FDA improperly waived a requirement for pediatric studies in connection with the 2000 Mifeprex approval.
- That FDA did not require the sponsor of Mifeprex to honor its commitments for Phase 4 studies.

We respond to each of these arguments below.

We note your petition challenges the original approval of Mifeprex in 2000, and therefore this response is addressed to the 2000 approval and to the labeling that was approved at that time. Today, the Agency is approving a supplemental NDA submitted by Danco Laboratories, LLC (Danco), the holder of the Mifeprex NDA. This supplemental NDA proposed modified labeling for Mifeprex, including an updated dosing regimen, and included data to support the new labeling. After reviewing Danco's supplemental NDA, FDA determined that it met the statutory standard for approval. The fact that the previously approved regimen is no longer included in the labeling does not reflect a decision that there were safety or effectiveness concerns with the previously approved regimen.

A. Approval of Mifeprex Was Consistent With Subpart H

You maintain that FDA's 2000 approval of Mifeprex under the subpart H regulations was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law, and thus violated the APA (Petition at 18-23). You state that pregnancy, without major complications, is not a serious or life-threatening illness; instead, you claim it is a normal physiological state experienced by most females one or more times and is rarely accompanied by life-threatening complications (Petition at 19). You contend that Mifeprex does not provide meaningful therapeutic benefit to patients over existing treatments because surgical abortion is a less dangerous, more effective alternative for the termination of pregnancy, and that Mifeprex does not treat any subset of the female population that is unresponsive to or intolerant of surgical abortion

(Petition at 21-23). Thus, you assert that the approval of Mifeprex did not meet the requirements for product approval under subpart H (Petition at 23).

We disagree with your conclusion that we inappropriately approved Mifeprex under subpart H. As stated in section I above, the accelerated approval regulations apply to new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (§ 314.500). As FDA made clear in the preamble to the final rule for subpart H, the subpart H regulations are intended to apply to serious or life-threatening conditions, as well as to illnesses or diseases.⁴ The Agency also made clear that a condition need not be serious or life-threatening in all populations or in all phases to fall within the scope of these regulations.⁵ Unwanted pregnancy falls within the scope of subpart H under § 314.500 because unwanted pregnancy, like a number of illnesses or conditions, can be serious for certain populations or under certain circumstances.

Pregnancy can be a serious medical condition in some women.⁶ Pregnancy is the only condition associated with preeclampsia and eclampsia and causes an increased risk of thromboembolic complications, including deep vein thrombophlebitis and pulmonary embolus. Additionally, there is a significant risk of a major surgical procedure and anesthesia if a pregnancy is continued; for 2013 (the most recent data available), the Centers for Disease Control and Prevention reported an overall 32.7 percent rate of cesarean sections in the United States.⁷ Other medical concerns associated with pregnancy include the following: disseminated intravascular coagulopathy (a rare but serious complication); amniotic fluid embolism; life-threatening hemorrhage associated with placenta previa, placenta accreta, placental abruption, labor and delivery, or surgical delivery; postpartum depression; and exacerbation or more difficult management of preexisting medical conditions (e.g., diabetes, lupus, cardiac disease, hypertension). In addition, approximately 50 percent of all pregnancies in the United States each year are unintended.⁸ According to the

⁴ See, e.g., 57 FR 58942, 58946 (Dec. 11, 1992).

⁵ Id.

⁶ According to data from the Centers for Disease Control and Prevention (CDC), for 2012 (the most recent year for which data are available), the pregnancy-related mortality ratio in the United States was 15.9 maternal pregnancy-related deaths per 100,000 live births. See CDC, Pregnancy Mortality Surveillance System, available on the CDC Web page at <http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html>. A 2012 study by Raymond and Grimes provides a comparison for the mortality rate associated with legal abortion to live birth in the United States for the earlier period from 1998 through 2005. Investigators reported that over the study period, the pregnancy related mortality rate among women who delivered live neonates was 8.8 deaths per 100,000 live births. This lower rate excludes deaths from ectopic pregnancies, stillbirths, gestational trophoblastic disease, etc. During the same period, the rate of abortion related mortality was 0.6 per 100,000 abortions. The risk of childbirth related death was therefore approximately 14 times higher than the rate associated with legal abortion. Raymond, EG and DA Grimes, Feb. 2012, The Comparative Safety of Legal Induced Abortion and Childbirth in the United States, *Obstet Gynecol*, 119 (2, Part 1):215-219.

⁷ See CDC, Nov. 5, 2014, Trends in Low-risk Cesarean Delivery in the United States, 1990-2013, National Vital Statistics Report, 63(6), available at http://www.cdc.gov/nchs/data/nvsr/nvsr63/nvsr63_06.pdf.

⁸ Guttmacher Institute, Feb. 2015, Unintended Pregnancy in the United States, at 1, available at <http://www.guttmacher.org/pubs/FB-Unintended-Pregnancy-US.pdf>. See also Institute of Medicine, 2011,

Institute of Medicine, women experiencing an unintended pregnancy may experience depression, anxiety, or other conditions.⁹

Furthermore, consistent with § 314.500, medical abortion through the use of Mifeprex provides a meaningful therapeutic benefit to some patients over surgical abortion.¹⁰ Although FDA provided several examples in the preamble to the final rule to illustrate how the term “meaningful therapeutic benefit” might be interpreted, the Agency did not suggest that the meaning of the term was limited to the examples provided.¹¹ In the Phase 3 clinical trial of Mifeprex conducted in the United States, medical termination of pregnancy avoided an invasive surgical procedure and anesthesia in 92 percent of the 827 women with an estimated gestational age (EGA) of 49 days or less.¹² Complications of general or local anesthesia, or of intravenous sedation (“twilight” anesthesia), can include a severe allergic reaction, a sudden drop in blood pressure with cardiorespiratory arrest, death, and a longer recovery time following the procedure. Medical (non-surgical) termination of pregnancy provides an alternative to surgical abortion; it is up to the patient and her provider to decide whether a medical or surgical abortion is preferable and safer in her particular situation.¹³

Clinical Preventive Services for Women: Closing the Gaps (Closing the Gaps), at 102-110, available at http://books.nap.edu/openbook.php?record_id=13181 (stating that “[u]nintended pregnancy is highly prevalent in the United States”).

⁹ See Closing the Gaps, *supra* note 8, at 103.

¹⁰ For a discussion of how FDA interprets the phrase “meaningful therapeutic benefit to patients over existing treatments” in 21 CFR 314.500, see FDA guidance for industry, *Expedited Programs for Serious Conditions—Drugs and Biologics*, at 3-4, 16-17, available on the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

¹¹ 57 FR 58942, 58947 (Dec. 11, 1992).

¹² FDA, 1999, Medical Officer’s Review of Amendments 024 and 033: Final Reports for the U.S. Clinical Trials Inducing Abortion Up to 63 Day Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments (Medical Officer’s Review), at 11 (Table 1) and 16, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf and http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P2.pdf. Spitz, IM, et al., 1998, Early Pregnancy Termination With Mifepristone and Misoprostol in the US, *NEJM*, 338:1241-1243.

¹³ CDC data indicate that for the 730,322 abortions reported in 2011, there were 2 deaths. The CDC’s calculated case fatality rate over the period from 2008 to 2011 (the most recent year for which data are available), the case fatality rate was 0.73 legal induced abortion-related deaths per 100,000 reported legal abortions. http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6410a1.htm?s_cid=ss6410a1_e. Mortality rates identified by type of abortion (medical or surgical) were not available. However, the evidence suggests that the risk of mortality associated with medical abortion is quite low. Confirmation of the low risk of medical abortion is provided in a study by Trussell, et al., which recorded no deaths for 711,556 medical abortions performed by Planned Parenthood clinics under the buccal misoprostol administration protocol (Trussell J, D Nucatola, et al., Mar. 2014, Reduction in Infection-Related Mortality Since Modifications in the Regimen of Medical Abortion, *Contraception*, 89(3):193-6). We note that one study reported a comparatively high occurrence of fatality (1 death in a study of 11,155 early medical abortions); however, this apparent high occurrence of fatality is likely due to instability in the estimate as a result of the small sample size (Goldstone P, J Michelson, et al., Sept. 3, 2012, Early Medical Abortion Using Low-Dose Mifepristone Followed by

You cite a study by Jensen, et al., as support for your claim that surgical abortion is less dangerous and more effective than Mifeprex (Petition at 21-22 (citing Jensen, JT, et al., 1999, Outcomes of Suction Curettage and Mifepristone Abortion in the United States: A Prospective Comparison Study, *Contraception*, 59:153-159 (Jensen study))). This study was a prospective, nonconcurrent cohort analysis comparing the patients from one site in the U.S. phase 3 trial and a separate group of patients (who were not part of the U.S. phase 3 trial) who underwent surgical abortion at the same facility. The populations that were compared were not randomized to treatment (i.e., medical or surgical abortion) and the treatment periods did not overlap.¹⁴ In addition, the data on medical abortion cited in the Jensen study are based on the 178 subjects at a single site in the phase 3 U.S. Mifeprex trial that enrolled 2,121 women. This small subset of the U.S. trial included patients with pregnancies of up to 63 days' gestation. Although you cite a surgical intervention rate of 18.3 percent in the Mifeprex patients, the surgical intervention rate for Mifeprex patients with an EGA \leq 49 days was 12.7 percent (9 of 71), which, because of the small number of patients in the two groups, is not statistically significantly different from the 3.9 percent rate for re-intervention in the comparative surgical group (3 of 77).¹⁵ Furthermore, the 3.9 percent who first had a surgical abortion and then required surgical re-intervention ultimately required *two* surgical interventions, not one, thereby exposing them twice to the risks inherent in invasive surgical procedures and anesthesia. Finally, although you state that the medical abortion patients in the Jensen study reported significantly longer bleeding than did surgical patients, there was not a greater amount of bleeding in the medical abortion group, nor was there a significant difference between the two treatment groups in the incidence of anemia as determined by the overall change in hemoglobin concentrations.

You state that FDA "viewed [s]ubpart H as the only available regulatory vehicle that had the potential to make Mifeprex safe" (Petition at 23 (footnote omitted)). The question of whether subpart H was "the only available regulatory vehicle" is not relevant here. As described above, Mifeprex met the criteria for approval under subpart H. Additionally, as stated in the September 28, 2000, memorandum to NDA 20-687 (Mifeprex Approval Memorandum), "the Population Council proposed and FDA agreed that this drug will be directly distributed via an approved plan that ensures the physical security of the drug to physicians who meet specific qualifications" that were set out in the approval letter and the Prescriber's Agreement.¹⁶

Buccal Misoprostol: A Large Australian Observational Study, *Med J Aust*, 197(5):282-6). Much more accurate and meaningful data are provided by Trussell's study covering >700,000 medical abortions.

¹⁴ We are not suggesting that in order to be adequate and well-controlled a trial must be concurrently controlled. As discussed below in section II.B.1, FDA's regulations in § 314.126 recognize a number of different types of controls.

¹⁵ In addition, the mean surgical intervention rate for all Mifeprex patients with gestational ages \leq 49 days in the Phase 3 U.S. trial was 7.9 percent (65 of 827 evaluable patients).

¹⁶ FDA, Sept. 28, 2000, Memorandum to NDA 20-687 MIFEPREX (mifepristone) Population Council (Mifeprex Approval Memorandum), available at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111366.pdf>

Furthermore, we approved a risk evaluation and mitigation strategy (REMS) for Mifeprex in June 2011, consisting of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.¹⁷ The 2011 REMS for Mifeprex incorporated the restrictions under which the drug was approved. Indeed, there is substantial overlap between the requirements of subpart H and the statutory criteria for REMS set out in Title IX.

Given all of the above, the Mifeprex NDA was appropriately approved in 2000.

B. The French and U.S. Clinical Trials of Mifeprex Provided Substantial Evidence to Support Approval

You contend that the studies on which the Population Council relied in support of its NDA for Mifeprex do not meet the statutory and regulatory requirements for the quality and quantity of scientific evidence needed to support a finding that a new drug is safe and effective (Petition at 24).

Our review of Mifeprex was thorough and consistent with the FD&C Act and FDA regulations, including the requirements under section 505(d) of the FD&C Act that: (1) there be adequate tests to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling (section 505(d)(1)) and (2) there be substantial evidence that the drug will have the effect it purports or is recommended to have under the conditions of use prescribed, recommended, or suggested in the labeling (section 505(d)(5)). The Mifeprex NDA was thoroughly reviewed, and the drug product was found to be safe and effective for its approved indication. In addition, as noted in the Mifeprex Approval Memorandum (at 1), FDA's Reproductive Health Drugs Advisory Committee (Advisory Committee) voted 6 to 0 (with 2 abstentions) on July 19, 1996, that the benefits of Mifeprex exceeded the risks. As set forth below, we disagree with your claims concerning the clinical trials that form the basis for the approval of Mifeprex.

1. The Clinical Trials Used to Support the Mifeprex NDA Were in Accordance With the FD&C Act and Applicable Regulations

You argue that because neither the French clinical trials nor the U.S. clinical trial of mifepristone were blinded, randomized, or concurrently controlled, these trials were inadequate to establish the safety and effectiveness of Mifeprex (Petition at 24-25 and 32-34). In addition, you assert in the response you submitted on October 10, 2003, to the comments in opposition to the Petition submitted by the Population Council and Danco (Response to Opposition) that the clinical trials of Mifeprex were not historically controlled but instead were uncontrolled.¹⁸ You state that the

¹⁷ 73 FR 16313 (Mar. 27, 2008).

¹⁸ Response to Opposition at 5. You also state that because the Mifeprex regimen was the first drug regimen that FDA approved to induce abortions, the applicant should have compared the new drug regimen to surgical abortions performed during the first 49 days after a woman's last menstrual period (Response to Opposition at

applicant did not describe any historical control group in the French clinical trials, and did not indicate that any of the scientific guidelines for selecting a proper control group before beginning a historically controlled study were used for these trials (id. at 5-6). You also reject the applicant's claim that the available information on surgical abortion constitutes historically controlled data (id. at 6).

We disagree with your conclusion that the French and U.S. clinical trials of mifepristone were not clinically and legally adequate to support the approval of Mifeprex. The data from these three clinical trials (a large U.S. trial and two French trials) constitute substantial evidence that Mifeprex is safe and effective for its approved indication in accordance with section 505(d) of the FD&C Act. The labeling approved in 2000 for Mifeprex was based on data from these three clinical trials and from safety data from a postmarketing database of over 620,000 women in Europe who had had a medical termination of pregnancy (approximately 415,000 of whom had received mifepristone together with misoprostol).¹⁹

The U.S. trial of Mifeprex involved 2,121 subjects enrolled at 17 sites. Of these, 827 had an EGA of ≤ 49 days and were included in the efficacy evaluation.²⁰ Medical termination of pregnancy was complete (without the need for surgical intervention) in 762 of these subjects (92 percent).²¹ Sixty-five of the subjects in the U.S. trial who were evaluable for efficacy were classified as having had a "treatment failure." The reasons for treatment failure (and number of subjects experiencing each) were: incomplete pregnancy termination ($n = 39$), still pregnant ($n = 8$), subject request for surgical intervention ($n = 5$), and medical indication (bleeding, $n = 13$).²² The two French trials enrolled a total of 1,681 subjects providing effectiveness outcomes. Among the French subjects, the success rate for medical termination of pregnancy was 95.5 percent.²³

In the U.S. trial, 859 subjects with an EGA of ≤ 49 days were evaluated for safety. Among these subjects, there were no deaths, one transfusion, and nine instances in which subjects received intravenous fluids.²⁴ The safety profile of the patient group in the French trials with an EGA of ≤ 49 days did not differ significantly from the safety profile of the same patient group in the U.S.

5, note 20). The fact that a drug might be the first one approved for a particular indication is not a factor in determining what type of control is adequate for a clinical trial of that drug for that indication. As discussed above, FDA's regulations provide for a variety of different types of controls (see 21 CFR 314.126(b)), and do not require comparison of a proposed drug product to an active control group to establish the safety and effectiveness of the drug. Therefore, the clinical trials to support the approval of Mifeprex were not required to have a surgical comparator arm.

¹⁹ Mifeprex labeling, Sept. 28, 2000, PRECAUTIONS, Teratogenic Effects: Human Data, *Pregnancy*, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf.

²⁰ Mifeprex Approval Memorandum, *supra* note 16, at 1; Medical Officer's Review, *supra* note 12, at 10.

²¹ Medical Officer's Review, *supra* note 12, at 11 (Table 1) and 16.

²² Id. at 11 (Table 1).

²³ Mifeprex Approval Memorandum, *supra* note 16, at 1.

²⁴ Medical Officer's Review, *supra* note 12, at 12-13.

trial, and the percentage of patients in the French and U.S. trials requiring hospitalization and blood transfusion and experiencing heavy bleeding was comparable.²⁵ There were no deaths in the French trials.²⁶

Section 505(d) of the FD&C Act states, in part, that FDA must refuse to approve an application if the Agency finds that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the drug's proposed labeling. Section 505(d) defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."

As stated in 21 CFR 314.126(a), the purpose of conducting clinical investigations of a drug is to distinguish the effect of the drug from other influences, such as a spontaneous change in the course of the disease or condition, placebo effects, or biased observation. Reports of adequate and well-controlled investigations serve as the main basis for determining whether there is substantial evidence to support the claims of effectiveness for a drug.

We agree that randomization and the use of concurrent controls are two principal means of ensuring that clinical trial data are reliable and robust. However, that does not mean that in order to be adequate and well-controlled, a clinical trial must use a randomized concurrent control design. Section 314.126(b) lists the characteristics of an adequate and well-controlled study. Contrary to your assertion (Petition at 24), FDA regulations do not require that a study be blinded, randomized, and/or concurrently controlled. Among the characteristics of an adequate and well-controlled study is that it uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect (§ 314.126(b)(2)). A historical control is one of the recognized types of control (§ 314.126(b)(2)(v)), and one in which the results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment in comparable patients or populations (*id.*). Unlike some other types of control (e.g., placebo concurrent control (§ 314.126(b)(2)(i)) or dose-comparison concurrent control (§ 314.126(b)(2)(ii))), use of a historical control does not include randomization or blinding. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances, including studies in which the effect of the drug is self-evident.²⁷ Thus, in the proper setting,

²⁵ *Id.* at 18.

²⁶ FDA, May 21, 1996, Statistical Review and Evaluation (May 21, 1996, Statistical Review), at 4 and 7, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_statr.pdf.

²⁷ 21 CFR 314.126(b)(2)(v). We note your contention that the effects of the regimen approved in 2000 are not self-evident because "[t]he Sponsor's focus on this dyadic set of possibilities (failure (0) or success (1)) obscures a whole range of less easily measurable, but critically important, outcomes," including "tissue retention, life-threatening hemorrhaging, persistent bleeding, infection, teratogenicity, pain, continued fertility, and psychological effects" (Response to Opposition at 8). We disagree with your argument. From a clinical perspective, there are two outcomes associated with the use of Mifeprex for medical abortion: either there is a complete abortion (without the need for surgical intervention) or there is not. The "outcomes" you

historically controlled trials can be considered adequate and well-controlled, and there is no need for the other types of control listed in § 314.126(b)(2).²⁸

The use of historical controls in the Mifeprex clinical trials was appropriate for two reasons. First, the natural history of a viable pregnancy is adequately documented (a pregnancy continues on average for 40 weeks' gestation).²⁹ Second, the effect of Mifeprex is dramatic, occurs rapidly following treatment, and has a low probability of having occurred spontaneously.³⁰ Furthermore, contrary to your assertion (Petition at 32-34), the use of a historical control in these circumstances is consistent with ICH's guidance for industry, *E10 Choice of Control Group and Related Issues in Clinical Trials* (E10 Guidance).³¹ The E10 Guidance addresses external controls (including historical controls) that are used in externally controlled trials to compare a group of subjects receiving the test treatment with a group of patients external to the study, rather than with an internal control group consisting of patients from the same population assigned to a different treatment.³² The guidance states that the "external control may be defined (a specific group of patients) or non-defined (a comparator group based on general medical knowledge of outcome)."³³

cite are complications that can be associated with all abortions (including surgical abortion, missed abortion (non-viable pregnancy that has not been expelled from the uterus), and spontaneous abortion).

²⁸ You cite to a statement in the May 21, 1996, Statistical Review regarding the two French trials that "[i]n the absence of a concurrent control group in each of these studies, it is a matter of clinical judgement whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy" (Petition at 27). FDA's finding that Mifeprex was safe and effective for its labeled indication was based on data from three trials, one in the U.S. and two in France, as well as from safety data from a database of over 620,000 women in Europe who had had a medical termination of pregnancy (and approximately 415,000 of whom had received the combination of mifepristone and misoprostol). The Medical Officer's Review, *supra* note 12, also states that the "U.S. clinical trials confirm the safety and efficacy of mifepristone and misoprostol found in the pivotal French studies for women seeking medical abortions with gestations of 49 days duration or less" (Id. at 18-19). As stated previously, it is up to the physician and his/her patient to decide whether a medical or surgical abortion is preferable and safer in the patient's particular situation.

²⁹ MacDonald, PC, NF Gant, et al., 1996, *Williams Obstetrics* (20th ed.), Appleton and Lange, at 151.

³⁰ Although sources and studies differ somewhat, the 92% success rate following mifepristone/misoprostol use far exceeds the rate of spontaneous abortion (spontaneous miscarriage). One source states: "No less than 30% and as much as 60% of all conceptions abort within the first 12 weeks of gestation, and at least half of all losses go unnoticed. Most recognized pregnancy losses occur before 8 weeks' gestation, and relatively few occur after 12 weeks" (Fritz, M and L Speroff, 2011, *Clinical Gynecologic Endocrinology and Infertility* (8th ed.), Lippincott Williams & Wilkins, Philadelphia, at 1193). Other sources indicate that 15% of all pregnancies between 4-20 weeks of gestation spontaneously abort (See Speroff, L, et al., 1989, *Clinical Gynecologic Endocrinology and Infertility* (4th ed.), Williams and Wilkins, Baltimore, at 535; see also Stenchever, MA, 2001, *Comprehensive Gynecology* (4th ed.), Mosby, at 414). According to the National Library of Medicine, "[a]mong women who know they are pregnant, the miscarriage rate is about 15-20%. Most miscarriages occur during the first 7 weeks of pregnancy." (Miscarriage, available on the MedlinePlus Web site at <http://www.nlm.nih.gov/medlineplus/ency/article/001488.htm>).

³¹ E10 Guidance, available on the FDA Drugs Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, at 6.

³² Id.

³³ Id.

Moreover, the E10 Guidance clearly states that, notwithstanding certain limitations of external controls, including the possibility of bias, external controls can be appropriate under circumstances where the effect of the treatment is dramatic and the usual course of the disease or condition is highly predictable.³⁴ In other words, historical controls can be appropriate in circumstances such as medical termination of early pregnancy. The use of the expected rate of spontaneous abortion during early pregnancy as the control in the Mifeprex clinical trials was appropriate and fully consistent with FDA regulations and guidance. The applicant could rely on the data from the three trials to support approval because they were adequate and well-controlled, using a historical control.³⁵

It is not uncommon for the drug product review divisions in FDA's Center for Drug Evaluation and Research (CDER) to accept for filing and approve applications that rely on clinical trials employing historical controls to support approval for drug products in which the outcome of the condition is well known and the effect of the drug is anticipated to be markedly different from that of a placebo. Examples include FDA's approval of numerous oncology drug products, including, for example, Xalkori (crizotinib) for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test, and Adcetris (brentuximab vedotin) for the treatment of patients with Hodgkin lymphoma and a rare lymphoma known as systemic anaplastic large cell lymphoma. Other examples include iPlex (mecasermin rinfabate [rDNA origin] injection) for treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH; Myozyme (alglucosidase ALFA) for use in patients with Pompe disease (GAA deficiency); Ferriprox (deferiprone) for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate; Voraxaze (glucarpidase) for treatment of toxic (>1 micromole per liter) plasma methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function; and Elelyso (taliglucerase alfa) for injection for use as a long-term enzyme replacement therapy in patients with Type 1 Gaucher disease. Similarly, it is not unusual for the CDER review divisions to accept for filing applications relying on historically controlled clinical trials. Examples of reproductive drug products for which a historical control is often relied on in the drug approval process include contraceptive drug products (e.g., most birth control pills, Mirena intrauterine device, NuvaRing (an intravaginal hormonal contraceptive), and Implanon (an implanted hormonal contraceptive)) and menopausal hormonal therapy products with the addition of a progestin to prevent endometrial cancer secondary to unopposed estrogen stimulation.

³⁴ Id. at 27.

³⁵ We disagree with your statement that the sponsor's failure to identify precisely a historical control group is fatal to its claim that the trials supporting the approval of Mifeprex were historically controlled (Response to Opposition at 5-6). In situations where an investigational product is anticipated to have an effect that is readily discernible and greatly exceeds that which would be expected otherwise, the historical control may be relied upon without explicitly describing it as such. Examples of situations where this arises include, as here, the use of a drug for early medical abortion, given that the majority of pregnancies continue to term, and the use of a drug as a contraceptive, given that the pregnancy rate in sexually active women between 18 and 35 years old in the absence of contraception for one year is well documented at approximately 85% (Hatcher, RA, et al., 2012, Contraception Technology (20th ed.), Ardent Media, Inc., at 780).

You state that FDA did not conduct a statistical review of the results of the U.S. clinical trial (Petition at 29). The Agency, however, concluded that the clinical results of the supporting U.S. clinical trial were “similar enough to the results of the European studies” (the studies used to support the original approval of Mifeprex in Europe) that a statistical evaluation of the results of the U.S. trial was not required.³⁶

You maintain that the Mifeprex approval is not in accordance with Agency guidance³⁷ on when only one effectiveness trial may be necessary for approval because: (1) mifepristone had not been approved for any use in any population in the United States and (2) no one had ever presented to FDA any evidence from adequate and well-controlled trials regarding any use for mifepristone.³⁸ As stated above, our approval of Mifeprex was based on not one but three studies that met the requirements of § 314.126. Therefore, Agency guidance concerning reliance on only one effectiveness trial is not relevant to the approval of Mifeprex.

You argue that FDA’s acceptance of the French and U.S. clinical trial data violated § 314.126(e), which states that uncontrolled studies or partially controlled studies are not acceptable as the sole basis for approval of claims of effectiveness (Petition at 34-36). As explained above, the Mifeprex clinical trials were neither uncontrolled nor partially controlled. They were historically controlled, and the use of an historical control was appropriate under § 314.126(b)(2)(v). Consequently, § 314.126(e) is inapplicable.

Citing § 314.500, you contend that the approval of Mifeprex under subpart H was improper because FDA did not require the concurrent testing of mifepristone with surgical abortion to test the proposition that mifepristone provides a meaningful therapeutic benefit over the standard method for terminating pregnancies (Petition at 37-40). You maintain that Mifeprex is the only drug that we have approved under § 314.520 (approval with restrictions to assure safe use) without requiring “that safety and efficacy be scientifically demonstrated through blinded, comparator-controlled, and randomized clinical trials” (Petition at 37).

Nothing in subpart H requires that an applicant conduct comparative clinical trials in order to demonstrate that a drug product provides meaningful therapeutic benefit to patients over existing treatments. Furthermore, nothing in the concept of “meaningful therapeutic benefit” requires concurrent testing of a proposed drug with an existing treatment.³⁹ We have approved other drugs

³⁶ FDA Memorandum to NDA 20-687 re: Statistical comments on Amendment 024, Feb. 14, 2000, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_statr.pdf.

³⁷ FDA guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (Effectiveness Guidance), available on the FDA Drugs Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

³⁸ Petition at 31-32 (citing Effectiveness Guidance at 5-17).

³⁹ You state that “[c]onducting a concurrently-controlled randomized trial comparing surgical abortion with the mifepristone-misoprostol regimen is readily achievable” (Petition at 32, note 145). You add that “[t]here are study designs that would have also allowed for blinding” (Id.). Assuming, arguendo, that it may have been feasible to design a randomized, concurrently-controlled study, such study was not required under our regulations; as described previously in this response, the clinical trials supporting the approval of Mifeprex

under subpart H based on clinical trials that do not directly compare the drug to an existing therapy, including Gleevec (imatinib mesylate), Tracleer (bosentan), and Xyrem (sodium oxybate). We also note that the latter two referenced drug products, Tracleer (bosentan) and Xyrem (sodium oxybate), were approved under the restricted distribution provisions at 21 CFR 314.520. As previously explained in this response, Mifeprex was deemed to have in effect an approved REMS under Title IX of FDAAA. The Mifeprex REMS, which was approved in June 2011 and is still in effect, incorporated the subpart H restrictions under which the drug was approved.

As evidenced by the foregoing, the studies supporting the 2000 approval of Mifeprex were consistent with the FD&C Act and FDA regulations, including § 314.126 and subpart H.

2. There Is No Need for an Audit of the French Clinical Data

You assert that FDA allowed “tainted data” to support the Mifeprex NDA by failing to require a comprehensive audit of the French clinical trial data after discovering violations of good clinical practices (Petition at 40-41). You maintain that we should therefore conduct a complete audit of all of the French clinical trial data to determine whether other trials must be conducted (Petition at 41 and 89).

We disagree with your characterization of both the French data and FDA’s reliance on that data. You reference the Form FDA 483 issued on June 28, 2006, to Dr. Elisabeth Aubeny, as well as the Summary of Findings related to that Form FDA 483. It is not uncommon to have trial sites receive a Form FDA 483, listing the FDA investigator’s observations regarding non-compliance with good clinical practice, at the conclusion of an inspection. The investigator will draft an Establishment Inspection Report (EIR) that reviews the violations noted and will recommend an action, taking into consideration the nature of the inspectional findings, any actions that occurred following the findings, and Agency policy. For products regulated by CDER, compliance reviewers in the Division of Clinical Compliance Evaluation in the Office of Scientific Investigations (previously, the Division of Scientific Investigations) review the EIR, the Form FDA 483, and the evidence collected during the inspection, as well as any written response submitted timely by the inspected party, to determine whether the recommended action is appropriate and is supported by adequate evidence. This review evaluates each violation’s effect on the timeliness, accuracy, and/or completeness of the data collected from the site to ascertain if the data are reliable. In this particular case, although there were violations cited on the Form FDA 483 and discussed in the EIR, the violations were determined not to affect the reliability of the data provided by that site. The statement you quote from the Summary of Findings reflects this conclusion. We note that, although the French studies were not performed under a U.S. investigational new drug application (IND), this is typical of many approved drugs that originally were developed or studied outside the United States, and is fully permissible under 21 CFR 312.120 (Foreign clinical studies not conducted under an IND) (including the version of the provision in effect at the time of the 2000

were historically controlled, which was appropriate under § 314.126(b)(2)(v). Furthermore, your suggestion that there are study designs that would have allowed for blinding raises ethical issues that go beyond the scope of your Petition and this response.

approval of Mifeprex). FDA concluded that the French trials were conducted in accordance with good clinical practice,⁴⁰ and the Agency was able to validate the data from those studies.

It is worth noting that in 1996, when the Advisory Committee reviewed the French data without considering the U.S. data, the committee voted 6 to 2 that the French data alone demonstrated efficacy and 7 to 0 (with one abstention) that the French data supported safety.⁴¹ The subsequent approval of Mifeprex was based not only on the data from the two French trials but also on the data from the large Phase 3 U.S. trial. The Advisory Committee received a report on the U.S. trial (the article by Spitz, et al., referenced in note 12 above) and had no comments.

For the foregoing reasons, there is no scientific or regulatory need for us to further review the French clinical data on Mifeprex.

3. Your Request for an Audit of the U.S. Clinical Data

In addition to your request that FDA conduct a full audit of the data from the French trials, you request that FDA conduct a full audit of all data from the U.S. trial (Petition at 1-2 and 89). Other than one footnote referring to a letter from the NDA sponsor to FDA (Petition at 89, note 384), you have provided no information supporting this request. Accordingly, we do not address this request further, other than to note that we do not believe there is any scientific or regulatory need to further review the U.S. clinical trial data relied on for approval of the Mifeprex NDA.

C. FDA Lawfully Approved Labeling for Mifeprex for Use with Misoprostol

You contend that FDA's "de facto" approval of misoprostol for use with Mifeprex as part of a medical abortion regimen was unlawful because the holder of the only approved NDA for misoprostol⁴² did not submit a supplemental NDA for this new use (Petition at 41-45). You further

⁴⁰ The regulations in effect at the time of the Mifeprex approval in 2000 refer to FDA accepting such studies when they are "well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community" FDA has generally interpreted that language as incorporating the principles of "good clinical practice" (see, e.g., ICH guidance for industry, *ICH E6 Good Clinical Practice: Consolidated Guidance* (E6 Guidance), available on the FDA Drugs Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>), which is the term used in the current regulations. The E6 Guidance states that GCP:

is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that clinical trial data are credible

(E6 Guidance at 1).

⁴¹ Mifeprex Approval Memorandum, *supra* note 16, at 1.

⁴² Two abbreviated new drug applications (ANDAs) for misoprostol have been approved since Mifeprex was approved: ANDA 076095 (IVAX Pharmaceuticals, Inc., approved July 10, 2002) and ANDA 091667 (Novel Laboratories Inc., approved July 25, 2012).

argue that FDA not only sanctioned, but participated in, the promotion of an off-label use of misoprostol by overseeing the creation of Mifeprex promotional materials that discuss the off-label use of misoprostol and by disseminating information about the off-label use in documents such as the press release announcing Mifeprex's approval (Petition at 46-47).

The approval of Mifeprex was based on evidence from three adequate and well-controlled clinical trials using the treatment regimen of administration of mifepristone on day one, followed approximately 48 hours later (i.e., on day three) by the administration of misoprostol (unless a complete abortion has already been confirmed before that time). Neither the FD&C Act nor FDA regulations require the submission of a supplemental NDA by the sponsor of the misoprostol NDA for the use of misoprostol as part of the approved treatment regimen for Mifeprex. In this situation, the "drug product" subject to section 505(b) of the FD&C Act (21 U.S.C. 355(d)) was Mifeprex.⁴³ The NDA for Mifeprex appropriately contained the full reports of investigations which have been conducted to show whether or not "such drug" is effective in use (§ 505(b)(1) of the FD&C Act), and FDA appropriately found that the Mifeprex NDA met the approval requirements in § 505(d) of the FD&C Act.

There are a number of drug products that FDA has approved as safe and effective in combination with another drug for a use that was not sought by the applicant of the second drug product, and for which the Agency did not require any change in the labeling of the second product (i.e., that the second product's labeling include the indication for use with the newly approved drug product). Examples of approved drug labeling that refer to the concomitant use of another drug without there being a specific reference to the combined therapy in the previously approved labeling for the referenced drug include the following:

- Xeloda (capecitabine) for treatment of metastatic breast cancer in combination with Taxotere (docetaxel) after failure of prior anthracycline-containing therapy⁴⁴

⁴³ In the Response to Opposition, you reference a July 2, 2002, letter submitted by the Population Council to Docket 01E-0363 re: Determination of Regulatory Review Period for Purposes of Patent Extension; Mifeprex (Response to Opposition at 12-13). In its July 2, 2002, letter, the Population Council made several statements regarding what it believed should be considered "the approved human drug product" for purposes of 21 CFR 60.22(a)(1), for purposes of patent term restoration. In the Agency's October 24, 2002, notice amending FDA's previous determination of the regulatory review period for Mifeprex (67 FR 65358), we addressed — and rejected — the Population Council's assertions. We stated that "[t]he applicant tries to characterize Mifeprex as mifepristone 'in combination with another active ingredient' in an attempt to take advantage of portions of the definition of 'human drug product' in 35 U.S.C. 156(f), that is, a human drug product means 'the active ingredient of a new drug * * * as a single entity or in combination with another active ingredient.' The applicant points to the definition of 'combination product' at 21 CFR 3.2(e) in this effort. A more useful description of a drug 'in combination with another active ingredient' is found at 21 CFR 300.50 (two or more drugs combined in a single dosage form). Mifeprex is not mifepristone 'in combination with another active ingredient.' Mifeprex is single entity mifepristone" (67 FR 65358, note 2).

⁴⁴ We note your assertion that when Xeloda and Taxotere are used together, each is being used for an FDA-approved use (Response to Opposition at 11). Taxotere (docetaxel) was approved on May 14, 1996; its current labeling states that it is indicated as a single agent for treatment of locally advanced or metastatic breast cancer after failure of prior chemotherapy, and in combination with doxorubicin and cyclophosphamide as adjuvant treatment of patients with operable node-positive breast cancer. Xeloda (capecitabine), which

- Nexium (esomeprazole magnesium) in combination with clarithromycin and amoxicillin for *H. pylori* eradication
- Persantine (dipyridamole) as an adjunct to coumarin anticoagulants for prevention of postoperative thromboembolic complications of cardiac valve replacement
- Herceptin (trastuzumab) in combination with paclitaxel for treatment of metastatic breast cancer
- Vistide (cidofovir) administered with probenecid for treatment of CMV retinitis in patients with AIDS
- Daraprim (pyrimethamine) for treatment of toxoplasmosis when used conjointly with a sulfonamide

You maintain that the labeling for Mifeprex is misleading because it directs physicians to use misoprostol for a purpose that FDA never approved and because it creates the false expectation that misoprostol is approved for medical abortion (Petition at 47). We disagree that the labeling for Mifeprex is misleading by virtue of the fact that it includes instructions for the use of misoprostol as part of the approved treatment regimen for Mifeprex. The Mifeprex labeling appropriately describes the clinical trial treatment regimen in which Mifeprex was shown to be safe and effective. The labeling for Mifeprex makes clear that Mifeprex tablets contain mifepristone, not misoprostol, and although the Indication and Usage section in the 2000 labeling does address the use of misoprostol in a regimen with Mifeprex, the labeling is clearly addressed to Mifeprex.

You claim that Mifeprex is misbranded because, per 21 CFR 201.6(a), the references to misoprostol in the Mifeprex labeling constitute a false or misleading representation that misoprostol itself is approved for medical termination of pregnancy (Petition at 48). In addition, you contend that Mifeprex is misbranded under section 502(j) of the FD&C Act (21 U.S.C. 352(j)) because it is unsafe when used as directed in the 2000 approved labeling (id.).

The references to misoprostol in the Mifeprex labeling do not render Mifeprex misbranded as described in § 201.6(a) because the labeling does not make any false or misleading representations with regard to misoprostol. We determined, and the labeling reflects, that Mifeprex is safe and effective for the termination of early pregnancy when used in combination with misoprostol. The approval was based on evidence from adequate and well controlled clinical trials in which misoprostol was administered two days after mifepristone to help stimulate uterine contractions; accordingly, the approved labeling describes the use of Mifeprex in combination with misoprostol.

originally was approved on April 30, 1998, for the treatment of metastatic breast cancer that is resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated, is currently approved (in addition to other indications) for use in combination with docetaxel for treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing chemotherapy. The indication to which this response refers is the concomitant use (i.e., use in combination) of the two drugs, a use that is not referenced in the labeling for Taxotere. Your arguments with respect to Actos (pioglitazone) in combination with a sulfonylurea, metformin, or insulin; Viread (tenofovir disoproxil fumarate) in combination with other antiretroviral agents; and Nexium (esomeprazole magnesium) in combination with clarithromycin and amoxicillin (id.) are similarly inapposite.

Additionally, the approved labeling in no way implies that misoprostol alone would be safe and effective for the termination of pregnancy. Thus, the statements in the labeling are neither false nor misleading with regard to the use of misoprostol.

With regard to section 502(j) of the FD&C Act, Mifeprex is not misbranded under that provision because, as discussed in the following section, the approved regimen for Mifeprex is not “dangerous to health when used in the dosage or manner; or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof.”

D. Mifeprex Is Safe for Its Approved Use and the Conditions of Approval Do Not Lack Essential Safeguards

You contend that FDA “approved mifepristone for use in a deregulated regimen that lacks key safeguards” (Petition at 5). You claim that in 2000, the Population Council repudiated distribution restrictions that it had proposed in 1996, and that FDA subsequently approved a regimen that does not embody restrictions sufficient to address legitimate safety concerns (Petition at 49). You note that the February 18, 2000, Mifeprex approvable letter stated that restrictions (per § 314.520) on the distribution and use of Mifeprex were needed to ensure safe use of the drug but that in March 2000, the Population Council said such restrictions were unwarranted (Petition at 51-52). You claim that we later yielded to the applicant on several important issues (Petition at 54-55).

FDA has found that Mifeprex is safe and effective for its intended use. It is true that, before the 2000 approval of Mifeprex, FDA and the applicant were not always in full agreement about the distribution restrictions. It is not unusual for such differences to emerge during the course of the review process for a proposed drug product. We ultimately determined that the distribution restrictions stated in the approval letter were appropriate to ensure the safety of Mifeprex for its intended use.⁴⁵ Three adequate and well-controlled clinical trials supported the safety of Mifeprex for its intended use, and over 15 years of postmarketing data and many comparative clinical trials in the United States and elsewhere continue to support the safety of this drug product.⁴⁶ Further, we approved a risk evaluation and mitigation strategy (REMS) for Mifeprex in June 2011, consisting of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Following is our response to the specific safety issues you raise in the Petition.

1. Ultrasound Dating

⁴⁵ We note your reference in your Response to Opposition to the statement by the Reproductive Health Drugs Advisory Committee that it had concerns about the distribution proposal discussed at the July 19, 1996, meeting (Response to Opposition at 4 (referencing the minutes from the 1996 Reproductive Health Drugs Advisory Committee meeting)). In light of FDA's determination in 2000 that the distribution restrictions stated in the approval were appropriate to ensure that Mifeprex was safe for its intended use, as well as the 2011 approval of the Mifeprex REMS, the Committee's reservations in 1996 are not applicable.

⁴⁶ See, e.g., Raymond, EG, et al., 2013, First-Trimester Medical Abortion With Mifepristone 200 mg and Misoprostol: A Systematic review, *Contraception*, 87:26-37 In this article, 87 trials were reviewed and 91 references were cited.

You maintain that the Mifeprex regimen is unsafe because it does not require ultrasound examination. Specifically, you maintain that the use of transvaginal ultrasound is necessary to accurately date pregnancies and to identify ectopic pregnancies, and you note both that Mifeprex was approved in 2000 only for women through 49 days' gestation and that it is contraindicated for women with a confirmed or suspected ectopic pregnancy (Petition at 57-61).

Although the protocol for the U.S. clinical trial required a transvaginal sonogram (TVS) for each patient at Visit 1 and stated that the test should be used "as indicated" at Visits 2 and 3, this does not mean that a TVS is essential to ensure the safe use of Mifeprex.⁴⁷ As stated in the Mifeprex Approval Memorandum, during the review process, the Agency carefully considered the role of ultrasound.⁴⁸ In the clinical trials, ultrasound was performed to ensure proper data collection on gestational age, but in clinical practice, pregnancies can also be (and frequently are) dated using other clinical methods. (As discussed in section II.F below, safeguards employed during clinical trials are not always essential for safe use of the approved drug product.) As part of the restricted distribution of Mifeprex put in place in 2000, each provider must have the ability to accurately assess the duration of pregnancy and to diagnose ectopic pregnancy. We determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy. These decisions should be left to the professional judgment of each provider, as no method (including TVS) provides complete accuracy. The approved labeling for Mifeprex recommended ultrasound evaluation as needed, leaving this decision to the judgment of the provider.

You claim that the only way to date a pregnancy accurately enough to exclude EGA > 49 days is by using TVS (Petition at 58). That is incorrect. As noted above, using TVS (or any other method) does not ensure complete accuracy in dating a pregnancy. In most cases, a provider can accurately make such a determination by performing a pelvic examination and obtaining a careful history, which would include the following: date of last menstrual period, regularity of menses, intercourse history, contraceptive history, and (if available) home pregnancy test results.⁴⁹ If in doubt, the provider can order an ultrasound and/or a blood test measuring the quantitative beta-human chorionic gonadotropin (hCG) to further assist in dating the gestational age.

Furthermore, use of a TVS does not guarantee that an existing ectopic pregnancy will be identified. As of April 30, 2015, there were 89 unduplicated reports in FDA's Adverse Event Reporting System (FAERS) database of ectopic pregnancy in women in the United States who had received mifepristone for termination of pregnancy since the approval of Mifeprex in the United States. In

⁴⁷ We note that the French clinical trials did not require an ultrasound examination; rather, the decision as to whether an ultrasound was needed was left to the discretion of the investigator.

⁴⁸ Mifeprex Approval Memorandum, *supra* note 16, at 5.

⁴⁹ See, e.g., Fielding, SL, et al., 2002, Clinicians' Perception of Sonogram Indication for Mifepristone Abortion up to 63 Days, *Contraception*, 66:27-31 (discussing the results of a prospective study of 1,016 women in a medical abortion trial at 15 sites that concluded that "clinicians correctly assessed gestational age as no more than 63 days in 87% of women. In only 1% (14/1013) of their assessments did clinicians underestimate gestational age. We conclude that the clinicians felt confident in not using ultrasound in most cases").

42.7% (38 of 89) of the reported cases, an ultrasound was completed. Of the 38 cases that had an ultrasound completed, 55.3% (21 of 38) showed no changes indicative of ectopic pregnancy.⁵⁰ In light of the fact that Mifeprex is contraindicated for women with a confirmed or suspected ectopic pregnancy, we believe it is reasonable to expect that the women's providers would not have prescribed Mifeprex if a pelvic ultrasound examination had clearly indicated an ectopic pregnancy; this strongly suggests, therefore, that ultrasound examinations were falsely negative for ectopic pregnancy in these women. The currently approved labeling for Mifeprex reflects this, stating that the "presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed Mifeprex."⁵¹

2. Physician Training and Admitting Privileges

You contend that the administration of Mifeprex should have been restricted to physicians who have formal training in both pharmaceutical and surgical abortion and who have admitting privileges to emergency facilities (Petition at 62-65).

Although we did not restrict the administration of Mifeprex to physicians with the specific requirements you list in your Petition, we did conclude in 2000 that Mifeprex had to be provided by a physician who, among other qualifications, either (1) has the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding or (2) has made plans to provide such care through other qualified providers and facilities.

During the clinical trials for Mifeprex, the principal investigators were trained in surgical abortions and were able to conduct any necessary surgical interventions.⁵² The protocol for the U.S. trial was designed such that the studies were conducted at 17 centers where the principal investigators could perform abortions by either vacuum aspiration or dilatation and curettage and had access to facilities that provided blood transfusions and performed routine emergency resuscitation procedures.

During the NDA review process, the issue of physician qualifications and certification was thoroughly discussed within the Agency, with the applicant, and with an outside consultant with expertise in early pregnancy termination. Although the distribution of Mifeprex was not restricted to any particular medical specialist, the Agency did determine in 2000 that certain restrictions were

⁵⁰ Seventeen cases were identified as having an ultrasound with a possible ectopic pregnancy. Fourteen of these 17 (82.3%) cases noted appropriate follow-up procedures, such as additional hCG monitoring, ultrasounds, appointments, or emergency room referral, while two cases did not include any additional follow-up information. In the remaining case, a diagnosis of a heterotopic gestation (simultaneous ectopic pregnancy and intrauterine pregnancy) was noted.

⁵¹ Mifeprex labeling (Mar. 29, 2016) available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#applist.

⁵² Additionally, it is common in drug development that the clinical investigators who conduct pivotal Phase 3 clinical trials have more specialized training than may be necessary to ensure the safe use of a drug post-approval. Examples are trials for male erectile dysfunction (typically conducted by urologists), hypertension (internists), depression (psychiatrists), and endometriosis (gynecologists).

necessary under § 314.520. In accordance with this determination, the Prescriber's Agreement for Mifeprex stated the following:⁵³

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have [sic] made plans to provide such care through others, and are [sic] able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex....

As noted in the Mifeprex Approval Memorandum, the requirement that a physician certify, by signing the Prescriber Agreement, that he or she has the qualifications described in that Agreement limited the physicians who would be eligible to receive Mifeprex from the sponsor to those who are familiar with managing early pregnancies.⁵⁴ Because only such qualified physicians would be using or would oversee the use of Mifeprex, we concluded that there was no need for special certification programs or additional restrictions. Additionally, as noted in the Mifeprex Approval Memorandum, in the U.S. clinical trial of Mifeprex, 11 out of roughly 850 patients needed surgical intervention to treat bleeding, and three of these patients were treated by non-principal investigators such as emergency room physicians and a non-study gynecologist.⁵⁵ These data suggested that patients would receive any needed surgical intervention from either their physician or another physician with the needed skills.⁵⁶ The Mifeprex Approval Memorandum also pointed out that the Mifeprex labeling and the Medication Guide approved at that time highlight that surgery may be needed and that patients must understand whether the provider will furnish any necessary medical intervention or whether they will be referred to another provider and/or facility.⁵⁷

In addition, one of the Phase 4 commitments accompanying the approval of Mifeprex was a cohort-based study of safety outcomes when Mifeprex is prescribed by physicians with the skills for surgical intervention compared to physicians who refer patients for surgical intervention. In a February 2008 submission, the applicant stated that so few medical abortions are prescribed by physicians who do not have surgical intervention skills that it was not feasible to do a meaningful

⁵³ Mifeprex labeling (June 8, 2011), Mifeprex (mifepristone) tablets, 200 mg, Prescriber's Agreement, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020687s014lbl.pdf.

⁵⁴ Mifeprex Approval Memorandum, *supra* note 16, at 5.

⁵⁵ *Id.*

⁵⁶ *Id.*

⁵⁷ *Id.*

study to assess this specific issue. After review of this submission, the Agency: (1) concurred with the applicant regarding the non-feasibility of conducting a meaningful study and (2) concluded that no differences between non-referrers or referrers in terms of clinical outcomes could be identified based on the data that had been submitted. Accordingly, on September 26, 2008, the Agency released the applicant from this commitment.

The provisions of the currently approved labeling (including the REMS) that relate to provider training and admitting privileges are substantially similar to the labeling provisions approved in 2000. Under current labeling, healthcare providers who administer Mifeprex must be licensed to prescribe, and must have the ability to date pregnancies accurately and to diagnose ectopic pregnancies. These healthcare providers must also (1) be able to provide any necessary surgical intervention, or (2) have made arrangements for others to provide for such care. Healthcare providers must be able to ensure that women have access to medical facilities for emergency care, and must agree to other responsibilities, including reviewing and signing the Patient Agreement Form with the patient and providing each patient with a copy of the signed Patient Agreement Form and the Medication Guide.⁵⁸

3. “Dear Health Care Provider” Letter and FDA “Mifepristone Questions and Answers”; Adverse Events Discussed in Response to Opposition

You maintain that your concerns about the safety of Mifeprex are validated by the April 19, 2002, “Dear Health Care Provider” letter issued by Danco and by statements in the “Mifepristone Questions and Answers” (Mifepristone Q&A) document (placed on FDA’s Web site on April 17, 2002) about reports of serious adverse events, including ruptured ectopic pregnancies and serious systemic bacterial infections (Petition at 65-71). You argue that FDA understated the possibility that the Mifeprex regimen caused the serious adverse events referred to in the letter and inappropriately attempted to link those events to the unapproved vaginal administration of misoprostol (Petition at 67-68).

The fact that Danco and FDA agreed that there was a need to issue a Dear Health Care Provider letter in April 2002 (or that a subsequent Dear Health Care Provider letter and a Dear Emergency Room Director letter were issued on September 30, 2004) does not imply that the approved Mifeprex regimen is unsafe. It is not uncommon for drug sponsors to issue “Dear Health Care Provider” letters, and, as noted in the Mifepristone Q&A document posted on our Web site in April 2002, “[w]hen FDA receives and reviews new information, the agency provides appropriate updates to doctors and their patients so that they have essential information on how to use a drug safely.”⁵⁹ The intent of the two “Dear Health Care Provider” letters and the “Dear Emergency Room Director” letter was to provide health care personnel with new safety information regarding the use of Mifeprex. Similarly, when these letters were issued, we posted Mifepristone Q&A documents to

⁵⁸ Mifeprex REMS, available at

<http://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=IndvRemisDetails.page&REMS=35>

⁵⁹ See Historical Information on Mifepristone (Marketed as Mifeprex), available at

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111334.htm>.

address questions that might arise as a result of the issuance of the letters. We disagree that we have in any way “inappropriately attempted to link” the adverse events to the intravaginal use of misoprostol. Rather, the April 2002 Mifepristone Q&A document accurately stated that in all of the adverse event cases at that time,⁶⁰ the misoprostol was given vaginally not orally; that we did not know what role, if any, the use of Mifeprex and vaginal misoprostol may have in the development of serious infections; and that FDA had not reviewed data on the safety and effectiveness of vaginal administration of misoprostol.

You maintain that it is particularly important for FDA to respond to these adverse events because the clinical trials in support of Mifeprex allegedly did not adhere to the Agency’s scientific methodology for such trials (Petition at 70). As explained above, however, the clinical trials supporting the approval of Mifeprex were adequate and well-controlled, and they provided substantial evidence of the safety and effectiveness of the drug product in accordance with the FD&C Act and FDA regulations.

In your Response to Opposition, you state that the serious adverse events reported to date are consistent with concerns expressed before approval (Response to Opposition at 16). You refer to the death of Holly Patterson on September 17, 2003, after she had taken Mifeprex and misoprostol to terminate her pregnancy. You state that Ms. Patterson’s apparent death from a serious systemic bacterial infection after taking Mifeprex is “not the first such death since FDA approved Mifeprex,” referring to a fatality due to serious systemic bacterial infection mentioned in the April 2002 “Dear Health Care Provider Letter” (Response to Opposition at 16-17). You also question whether adverse events for Mifeprex will be adequately reported to FDA (Response to Opposition at 18).

As with all approved drug products, we continue to monitor the safety of Mifeprex. Since the approval of Mifeprex, the Agency has issued two public health advisories (one in July 2005⁶¹ and one in March 2006⁶²) and posted multiple MedWatch safety alerts (in November 2004⁶³ and July 2005, the latter with updates in November 2005 and March 2006⁶⁴). As referenced above, Danco has issued two Dear Health Care Provider letters and one Dear Emergency Room Director letter. Furthermore, since you submitted your Response to Opposition, Danco has revised the labeling for

⁶⁰ The April 2002 Mifepristone Q&A document refers to cases of ectopic pregnancy, sepsis, and heart attack.

⁶¹ Available at, <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051734.htm>.

⁶² Available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051196.htm>.

⁶³ Available at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm166463.htm>.

⁶⁴ Available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111339.htm>.

Mifeprex (including the prescribing information, the Medication Guide, and the Patient Agreement), in November 2004, December 2004, July 2005, and April 2009⁶⁵ to provide prescribers and women with additional information about infection, vaginal bleeding, and ectopic pregnancy.

The boxed warning for Mifeprex currently states the following:

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use. No causal relationship between the use of MIFEPREX and misoprostol and these events has been established.

- **Atypical Presentation of Infection.** Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis.
- **Bleeding.** Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding.

Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the MIFEPREX REMS Program.

Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting or diarrhea) for more than 24 hours after taking misoprostol.

Advise the patient to take the Medication Guide with her if she visits an emergency room or a healthcare provider who did not prescribe MIFEPREX, so that the provider knows that she is undergoing a medical abortion.

⁶⁵ The Mifeprex labeling also was revised in June 2011 when the REMS was approved. In addition, as described above, FDA is today approving a supplemental NDA submitted by Danco that proposed modified labeling for Mifeprex. See Mifeprex labeling (Mar. 29, 2016) available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#applist.

The WARNINGS section of the Mifeprex labeling states, in part, the following:

[With respect to infection and sepsis:]

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established.

Clostridium sordellii infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

[With respect to uterine bleeding:]

Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion.

Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.

Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in women who bleed heavily.

Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfusions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to ≤ 0.1% of subjects. Because heavy bleeding requiring surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

[With respect to ectopic pregnancy:]

MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies. Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.

Women who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

The Agency has regularly completed a cumulative summary of U.S. postmarketing adverse events reported for the use of mifepristone for medical termination of pregnancy. From the approval date of Mifeprex (September 28, 2000) through October 31, 2012, we received 2,740 reports of adverse events associated with the use of mifepristone in the United States to terminate pregnancy,⁶⁶ including 57 reports of severe infections⁶⁷ and 416 incidences of blood loss requiring transfusion. From November 1, 2012, through April 30, 2015, we received 984 reports of adverse events associated with the use of mifepristone in the United States to terminate pregnancy, including 9 reports of severe bacterial infections and 134 incidences of blood loss requiring transfusion.⁶⁸ As of April 30, 2015, 89 ectopic pregnancies associated with the use of mifepristone in the United States had been reported since the approval of Mifeprex. As of July 24, 2015, 17 U.S. deaths had been reported since the approval of Mifeprex. Deaths were associated with sepsis in 8 of the 17 reported fatalities (7 cases tested positive for *Clostridium sordellii*, and 1 case tested positive for *Clostridium perfringens*).⁶⁹ Seven of the eight fatal sepsis case reported vaginal misoprostol use;

⁶⁶ This represents data from the FDA's previous adverse event reporting system, which was known as AERS.

⁶⁷ Severe infections generally involve death or hospitalization for at least 2-3 days, intravenous antibiotics for at least 24 hours and total antibiotic usage for at least 3 days, and any other physical or clinical findings, laboratory data or surgery that suggest a severe infection.

⁶⁸ This represents data from the current FDA Adverse Event Reporting System (FAERS), which was implemented in September 2012 and replaced AERS. FDA migrated all of the data from the previous reporting system (AERS) to FAERS. FDA validated and recoded product information as the reports from the AERS database were migrated to the FAERS database. In addition, the FAERS database features a new search functionality that is based on the date FDA initially received for the case; this facilitates more accurate follow-up for cases that have multiple reports and multiple receipt dates. For these reasons, there may be differences in the case counts between AERS and FAERS.

⁶⁹ We note your statements in your October 10, 2003, Response to Opposition Comments that the presence of retained products of conception can lead to the development of intrauterine or systemic infection and that Mifeprex might potentiate this possibility through negative effects on immune system function or normal protective mechanisms (Response to Opposition at 17). Regarding retained products of conception and the emergence of infections, based on autopsy and/or ultrasound reports, there were no retained products of conception in any of the eight deaths associated with infections (sepsis). With respect to your claim that Mifeprex might increase the likelihood of infection by adversely affecting immune system function, although

one case reported buccal misoprostol use. Seven of the nine remaining U.S. deaths involved two cases of ruptured ectopic pregnancy and one case each of the following: substance abuse/drug overdose; methadone overdose; suspected homicide; suicide; and a delayed onset of toxic shock-like syndrome. In the eighth case, the cause of death could not be established despite performance of an autopsy; tissue samples were negative for *C. sordellii*. In the ninth case, infection was ruled out and the final autopsy report listed pulmonary emphysema as the cause of death.⁷⁰

We disagree with your assertion that adverse event reporting for Mifeprex is "spotty" and that, as a result, the database for post-approval adverse events for Mifeprex is incomplete (Response to Opposition at 18). You are correct that reporting to the Agency's MedWatch program is voluntary, and we acknowledge that there is always a possibility with any drug that some adverse events are not being reported. We believe, however, that the potential for underreporting of serious adverse events associated with the use of Mifeprex for medical abortion has been very low because of the restricted distribution of the product and because healthcare providers have agreed in writing to report any hospitalizations, transfusions, or other serious adverse events associated with the drug to the sponsor, which is required under FDA's regulations to report all adverse events, including serious adverse events, to the Agency (see 21 CFR 314.80, 314.81). As with all drugs, we will continue to closely monitor the postmarketing safety data on Mifeprex.

published experimental data from animal models suggest that this is a theoretical possibility, the overall event rate of serious infections does not support this. If Mifeprex were adversely affecting immune system function, we would expect to see a much higher rate of serious infections from more common organisms, as well as a higher number of deaths in Europe (where mifepristone has been approved for over 24 years) and in the United States. Contrary to your statements, data from the medical literature and findings by the CDC suggest that the critical risk factor in the reported cases of sepsis is pregnancy itself (see Miech, RP, 2005, Pathophysiology of Mifepristone-Induced Septic Shock Due to *Clostridium sordellii*, Ann Pharmacother, 39:1483-1488). In May 2006, FDA, along with the CDC and the National Institute of Allergy and Infectious Diseases at the National Institutes of Health held a workshop on emerging clostridial disease. The issue of immunosuppression also was discussed at length during this public workshop. It was clear from the presentations at the workshop that *C. sordellii* causes rapid and serious clinical illness in settings other than medical abortion, including among pregnant women who have recently undergone spontaneous abortion or term delivery. The fact that cases of *C. sordellii* have been identified both in pregnant women who have undergone medical abortion and those who have not supports the idea that the physiology of pregnancy may be a more plausible risk factor for *C. sordellii* illness than having undergone a medical abortion with Mifeprex.

⁷⁰ FDA is aware of 11 additional deaths of women in foreign countries who used mifepristone for the termination of pregnancy. This included one death associated with sepsis (*Clostridium sordellii* identified in tissue samples) in a foreign clinical trial, and 10 deaths identified from post-marketing data. These 10 fatal cases were associated with the following: sepsis (Group A *Streptococcus pyogenes*); a ruptured gastric ulcer; severe hemorrhage; severe hemorrhage and possible sepsis; "multivisceral failure"; thrombotic thrombocytopenic purpura leading to intracranial hemorrhage; toxic shock syndrome (*Clostridium sordellii* was identified through uterine biopsy cultures); asthma attack with cardiac arrest; respiratory decompensation with secondary pulmonary infection 30 days after mifepristone in a patient on the lung transplant list with diabetes a jejunostomy feeding tube, and severe cystic fibrosis; *Clostridium septicum* sepsis (from a published literature report).

E. Withdrawal of the Approval for Mifeprex Based on Current Use Is Not Appropriate

You claim that Mifeprex abortion providers have disregarded the restrictions in the approved regimen “without any reaction from FDA, the Population Council, or Danco” (Petition at 71). You also claim that “common departures from the approved regimen” have included (1) offering the regimen to women with pregnancies beyond 7 weeks and (2) eliminating the second of the three prescribed visits to the health care provider (Petition at 72-74). You argue that we should withdraw approval of Mifeprex under § 314.530(a)(4) due to the failure of the Population Council and Danco to adhere to the postmarketing restrictions in the approval letter (Petition at 71).

In the Response to Opposition, you suggest that some providers have not met their obligations because many prescriber Web sites (1) advertise the Mifeprex regimen as being available for patients whose pregnancies have progressed beyond 49 days and (2) indicate that patients take misoprostol at home rather than at the provider’s office (Response to Opposition at 19-20). Thus, you maintain that many prescribers have allowed patients to make false statements and that the applicant is obligated to stop sales to these prescribers (*id.* at 20). You claim that prescribers have disregarded the requirements imposed with the 2000 approval of Mifeprex to provide patients with the Medication Guide, obtain their signatures on the Patient Agreement, and give them the opportunity to read and discuss these documents (*id.* at 20-21). You state that because some prescribers, with the applicant’s tacit approval, have permitted patients to sign the Patient Agreement while effectively directing them not to adhere to its requirements, the applicant cannot be described as meeting its obligations (*id.* at 21).

FDA is aware that medical practitioners may use modified regimens for administering Mifeprex and misoprostol. However, FDA does not believe that it is appropriate to initiate proceedings under 21 CFR 314.530 or section 505(e) of the FD&C Act to withdraw the approval of Mifeprex based on available information regarding the distribution of Mifeprex.

The Mifeprex approval letter included nine items that the applicant and/or prescriber were obligated to follow. As stated earlier in this response, Mifeprex has been subject to a REMS which incorporated these restrictions, including by appending a Prescriber’s Agreement outlining required qualifications and guidelines prescribers must agree to follow. Specifically, the Prescriber’s Agreement required each physician to attest to possessing certain necessary skills and abilities related to managing early pregnancy to ensure safe use of the drug.⁷¹ The Prescriber’s Agreement also contained responsibilities that prescribers must carry out.⁷² The Prescriber’s Agreement stated that prescribers must have read and understood the prescribing materials.⁷³

⁷¹ Prescriber’s Agreement, *supra* note 53, at 1.

⁷² *Id.* at 1-2.

⁷³ *Id.* at 1.

The 2000 Prescriber's Agreement also required that the prescriber (1) provide each patient with a copy of the Medication Guide and the Patient Agreement, (2) fully explain the procedure to the patient, and (3) give the patient the opportunity to read and discuss the Medication Guide and Patient Agreement.⁷⁴ The Medication Guide and the Patient Agreement stated the approved dosage and administration of Mifeprex. FDA has no evidence, nor have you provided any evidence, that prescribers have not signed the Prescriber's Agreement, or that women either have not been given the opportunity to read and discuss the Patient Agreement or have not signed the Patient Agreement.

As noted above, restrictions on the distribution and use of Mifeprex substantially similar to those approved in 2000 remain in place today.

F. Safeguards Employed in Clinical Trials Are Not Necessarily Essential Conditions for Approval

You maintain that we effectively approved a drug regimen that we had not tested because the Mifeprex regimen approved in 2000 does not include important safeguards employed in the U.S. clinical trial (e.g., governing physician training, use of ultrasound, 4-hour post-misoprostol monitoring, physician privileges at facilities that provide emergency care) (Petition at 75-76). You argue that we should not have extrapolated conclusions about the safety and effectiveness of the Mifeprex regimen from data generated under trial conditions that do not mirror the approved regimen (*id.*).

We disagree with your assertions. Furthermore, your implication that the approved conditions of use for a drug product must mirror those used in the clinical trials supporting its approval is incorrect. As discussed above with respect to ultrasound dating and physician qualifications, safeguards employed in clinical trials are often not reflected in approved drug product labeling nor are they necessarily needed for the safe and effective use of the drug product after approval. Many clinical trial designs are more restrictive (e.g., additional laboratory and clinical monitoring, stricter inclusion and exclusion criteria, more visits) than will be necessary or recommended in postapproval clinical use; this additional level of caution is exercised until the safety and efficacy of the product is demonstrated. For example, in menopause hormonal therapy trials, specialists perform periodic endometrial biopsies to establish the safety of long-term hormone use. Once the safety of the product has been established, these biopsies are not recommended in the approved product labeling, nor are they routinely performed in actual use with the approved product. During our review of the clinical data submitted in support of an NDA, we make an assessment of the procedures employed during the clinical trials and the conditions under which the drug was studied. This assessment is reflected in the approved labeling for the drug product.

Upon reviewing the data submitted in support of the Mifeprex NDA, we concluded in 2000 that restrictions requiring ultrasound dating of gestational age of the pregnancy and limiting access to Mifeprex to physicians trained in surgical abortions and capable of performing surgical intervention if complications arise subsequent to use of Mifeprex were not necessary to ensure its safe use (see discussion in section II.D above).

⁷⁴ *Id.*

G. FDA Appropriately Concluded That Studies of Mifeprex in Pediatric Patients Were Unnecessary

You maintain that our 2000 approval of Mifeprex violated regulations requiring that new drugs be tested for safety and effectiveness in the pediatric population (Petition at 76). You state that although we stated in the September 28, 2000, approval letter that the application was subject to the Pediatric Rule (21 CFR 314.55), we waived the requirement without explanation (Petition at 78). You contend that the Mifeprex application was not in accordance with any of the three provisions under which an applicant may obtain a waiver under 21 CFR 314.55(c)(2) of the pediatric study requirement, for the following reasons:

- 21 CFR 314.55(c)(2)(i) does not apply because FDA maintained that Mifeprex represented a meaningful therapeutic benefit over existing treatments and because Mifeprex can be expected to be used in a substantial number of pediatric patients.
- 21 CFR 314.55(c)(2)(ii) does not apply because pediatric studies of Mifeprex would not have been either impossible or highly impractical because a large population of pediatric females becomes pregnant each year and the female population is evenly distributed throughout the country.
- 21 CFR 314.55(c)(2)(iii) does not apply because FDA stated that there was no reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen than older females (Petition at 79-82).

As an initial matter, we reject your contention that the Population Council did not provide evidence from any adequate and well-controlled adult studies of Mifeprex, and that therefore it was inappropriate to rely on the submitted adult studies under § 314.55(a) with respect to the use of Mifeprex in the pediatric population (Petition at 82). As discussed above, the Mifeprex approval was based on three adequate and well-controlled clinical trials.

Our conclusion that studies of Mifeprex in pediatric patients were not needed for approval was consistent with FDA's implementation of the regulations in effect at that time.⁷⁵ We determined that there were sufficient data from studies of mifepristone. Therefore, the Mifeprex approval letter should have stated our conclusion that the pediatric study requirements were waived for pre-menarchal patients and that the pediatric study requirements were met for post-menarchal pediatric patients, rather than stating that we were waiving the requirements for all pediatric age groups.⁷⁶

⁷⁵ FDA was enjoined from enforcing 21 CFR § 314.55 under *Ass'n of Am. Physicians & Surgeons v. FDA*, 226 F. Supp. 204 (D.D.C. 2002). However, on December 3, 2003, the President signed into law the Pediatric Research Equity Act of 2003 (PREA 2003), Public Law 108-155, which gave FDA the statutory authority to require pediatric studies of drugs when such studies are needed to ensure the safe and effective use of drugs in children. PREA 2003 stated that any waivers or deferrals that were granted under the Pediatric Rule were considered to be granted under PREA 2003 (see Section 4 of Public Law 108-155).

⁷⁶ FDA's implementation of the Pediatric Rule was still at a relatively early stage in September 2000 and the Agency was not always precise regarding the language used in approval letters to distinguish between situations where studies were waived and where studies were not needed because the requirements were met.

It is still our scientific opinion, based on the medical literature and over 15 years of use in the United States, that there is no biological reason to expect menstruating females under age 18 — compared to women age 18 and older — to have a different physiological outcome with the Mifeprex regimen.⁷⁷

H. The Mifeprex Approval Letter Included Appropriate Phase 4 Commitments

You state that although the Population Council agreed in 1996 to perform Phase 4 studies with six different objectives, the Mifeprex approval letter included only two Phase 4 study obligations (Petition at 85-86). You allege that the changes in its Phase 4 commitments were largely in response to the Population Council's unwillingness to explore the "ramifications" of the Mifeprex regimen (Petition at 87). You maintain that this alleged "curtailment" of Phase 4 study commitments was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law (Petition at 88).⁷⁸

We disagree with your assertions. Our process for determining the appropriate Phase 4 studies for Mifeprex adequately addressed our concerns and reflected typical Agency-applicant interactions to reach consensus on appropriate postmarketing studies.⁷⁹ It is common for proposed Phase 4 commitments to evolve during the application review process. As you note (Petition at 85), in 1996, the Population Council committed to six postmarketing studies with the following objectives:

⁷⁷ In the Mifeprex Approval Memorandum, the Office Director stated, "FDA agrees there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Spitz data actually suggests a trend towards increased success of medical abortion with younger patients" (Mifeprex Approval Memorandum, *supra* note 16, at 7).

⁷⁸ We note that post-marketing studies are not required for approvals under 21 CFR 314.520.

⁷⁹ You also state that, "[a]s a general rule, the clinical trials required by FDA to support an NDA are adequate to establish short-term drug safety and effectiveness. The standard pre-approval clinical trials, however, are typically incapable of providing either the amount or type of data necessary to assess a drug's long-term effects" (Petition at 84). This argument is not relevant to Mifeprex, which is approved for medical termination of pregnancy. Mifeprex is not approved for long-term or chronic use, which is an important factor in assessing the need to study long-term effects of a drug. Long-term safety for a single-dose medication is generally not a concern. However, FDA routinely monitors postmarketing safety data for all approved drugs. Mifeprex is no exception. FDA's Office of Surveillance and Epidemiology continuously monitors available safety data from use of mifepristone for termination of pregnancy both within and outside of the United States and has not identified any long-term safety signals. The Mifeprex adverse events reported are consistent with product labeling and with what can be expected with spontaneous and surgical abortions. Furthermore, as explained in this response, since Mifeprex's approval, safety concerns and adverse events have been monitored through enhanced surveillance and reporting by certified prescribers, and we have required a REMS for Mifeprex including a Medication Guide, elements to assure safe use, an implementation system that requires the sponsor to assess the performance of certified distributors, and a timetable for submission of assessments of the REMS. We also continue to closely monitor the post-marketing safety of mifepristone for termination of pregnancy for any new or long-term signals.

- (1) Monitor the adequacy of the distribution and credentialing system.
- (2) Follow-up on the outcome of a representative sample of Mifeprex-treated women who have surgical abortion because of method failure.
- (3) Assess the long-term effects of multiple use of the regimen.
- (4) Ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.
- (5) Study the safety and efficacy of the regimen in women under age 18, women over age 35, and women who smoke.
- (6) Ascertain the effect of the regimen on children born after treatment failure.

As stated in the Mifeprex Approval Memorandum (at 7), during the final review of the Mifeprex NDA in 2000, items 1, 2, 4, and 5 above were revised and integrated into a single Phase 4 study to assess whether, for providers who did not have surgical intervention skills and referred patients for surgery, clinical outcomes were similar to those of patients under the care of physicians (such as those in the clinical trials) who possessed surgical skills. Based on a revised protocol, this Phase 4 study would monitor the adequacy of provider qualifications (item 1) and collect data on safety outcomes and method failures (item 2) and return of patients for their follow-up visits (item 4). Because patients would not be restricted to a specific age range or smoking status, information to address item 5 also would be obtained. In a second Phase 4 study, the applicant would examine the outcomes of ongoing pregnancies (i.e., method failures) through a surveillance, reporting, and tracking system (item 6). Thus, although the approval letter listed only two Phase 4 studies, those two studies incorporated all but one element of the six studies listed in the September 18, 1996, approvable letter concerning the Mifeprex NDA. (As discussed below, the remaining study was not included for logistical and practical reasons.)

As mentioned in section II.D.2 above, for the first Phase 4 study, which addressed items 1, 2, 4, and 5 above, the applicant reported in a submission in February 2008 that so few medical abortions are prescribed by physicians who do not have surgical intervention skills that it was not feasible to do a meaningful study to assess this specific issue. We agreed with the applicant regarding the non-feasibility of conducting a meaningful study and concluded that no differences between non-referrers or referrers in terms of clinical outcomes could be identified based on the data that had been submitted. In September 2008, we released the applicant from this postmarketing commitment.

For the second Phase 4 study, which addressed item 6 above, based on the reporting of ongoing pregnancies during the first 5 years of Mifeprex distribution, the applicant provided updates in January 2006 and November 2007. Danco reported that only one to two pregnancies per year were followed for final outcomes, and explained that the small number was due, in part, to the requirement that the patients consent to participation after seeking a pregnancy termination. In January 2008, because of the lack of an adequate number of enrolled women, and based on subsequent reports, we released the applicant from this postmarketing commitment.

In addition, as noted in the Mifeprex Approval Memorandum (at 7), we agreed with the Population Council both that it would not be feasible to identify and enroll sufficient numbers of repeat users of the drug and that the pharmacology of mifepristone does not suggest any carryover effect after one-time administration. Accordingly, we did not include item 3 as a Phase 4 commitment in the September 28, 2000, approval letter. However, we note that data from many other studies reported in the medical literature using mifepristone for, e.g., fibroids, uterine myoma, meningioma, psychiatric illnesses, and Cushing's disease, in much higher daily and lower daily doses for chronic use (months) have not raised any major safety issues.⁸⁰

III. REQUEST FOR STAY AND REVOCATION OF APPROVAL

You request that we immediately stay the approval of Mifeprex, thereby halting all distribution and marketing of the drug pending final action on your Petition (Petition at 2). You cite 21 CFR 10.35 as the basis for your request for a stay (Petition at 1). In addition, you urge us to revoke the approval of Mifeprex because of the purported legal violations and safety concerns set forth in your Petition (Petition at 2).

As described above, we are denying your Petition. Therefore, your request for a stay pending final action on your Petition is moot.

For the reasons set forth in section II of this response, we conclude that you have not presented any evidence that the applicable grounds in 21 CFR 314.530 have been met with respect to Mifeprex. Furthermore, you have not provided any evidence that any of the applicable grounds in section 505(e) of the FD&C Act have been met for Mifeprex.⁸¹ Therefore, you have not provided any evidence that would serve as a basis for seeking to withdraw the approval of Mifeprex.

⁸⁰ See, e.g., Tristan, M, et al., 2012, Mifepristone for Uterine Fibroids (Review), Cochrane Library, 8:1-47; Esteve, JL, et al, 2013, Mifepristone Versus Placebo To Treat Uterine Myoma: A Double-Blind, Randomized Clinical Trial, *Int J Womens Health*, 5:361; Spitz, IM, et al., 2005, Management of Patients Receiving Long-Term Treatment With Mifepristone, *Fertil Steril*, 84:1719; Blasey, CM, TS Block, JK Belanoff, and RL Roe, 2011, Efficacy and Safety of Mifepristone for the Treatment of Psychotic Depression, *J Clin Psychopharmacol*, 31:436; [Fleseriu, M, et al., 2012, Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome, *J Clin Endocrinol Metab*, 97:2039.](#)

⁸¹ You have not presented any clinical data or other information demonstrating that Mifeprex is unsafe for use under its approved conditions for use, either on the basis of evidence available to the Agency at the time of approval or when also considering evidence obtained subsequent to approval. In addition, you have not provided any new evidence that, when evaluated with the evidence available at the time of Mifeprex's approval, shows that there is a lack of substantial evidence that the drug will have its intended effect.

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IV. CONCLUSION

We appreciate and share your concerns about the need to appropriately manage the risks associated with the use of Mifeprex. Our concerns about the potential complications associated with Mifeprex led to its approval in accordance with 21 CFR 314.520. It was deemed to have in effect a REMS in 2007, and it has had an approved REMS since 2011.⁸²

For the reasons set forth above, your request that we immediately stay the approval of Mifeprex is moot, and we deny your request that we revoke approval of the Mifeprex NDA. In addition, we deny your request that we conduct an audit of all records of the French and U.S. clinical trials supporting the Mifeprex approval. As with all approved new drug products, we will continue to monitor the safety of Mifeprex and take any appropriate actions.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. Woodcock', with a stylized, flowing script.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research

⁸² As of today's approval of Danco's supplemental NDA, the Medication Guide is no longer part of the REMS. However, the Medication Guide will remain as part of approved patient labeling and will be required to be provided to the patient under current Medication Guide regulations.

EXHIBIT 23

2016 FDA Letter to Danco Labs



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020687/S-020

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (4), (b) (6)

P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated May 28, 2015, received May 29, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated July 17, 2015.

This "Prior Approval" supplemental new drug application proposes to provide for use through 70 days gestation, revise the labeled dose and dosing regimen and modify the REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pre-menarcheal patients because the use of this product before menarche is not indicated, and we have determined that you have fulfilled the pediatric study requirement for post-menarcheal patients.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Mifeprex (mifepristone) Tablets was originally approved on June 8, 2011. The REMS consisted of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS included revisions to both the prescriber and patient agreement forms.

Other changes proposed in the efficacy supplement prompted additional revisions to the Mifeprex REMS materials. During review of this efficacy supplement, we also assessed the current REMS program to determine whether each Mifeprex REMS element remains necessary to ensure that the drug's benefits outweigh the risks.

After consultations between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), we have determined that the approved REMS for Mifeprex should be modified to continue to ensure that the benefits of Mifeprex outweigh its risks and to minimize the burden on the healthcare delivery system of complying with the REMS. The REMS modifications submitted by you on March 29, 2016 are approved.

We have determined that it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Mifeprex outweigh its risks. The

Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted on July 17, 2015, and appended to this letter, is approved as amended. The modified REMS consists of elements to assure safe use (A, C and D), an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on June 8, 2011.

The REMS assessment plan will include the information submitted to FDA on March 29, 2016.

The revised REMS assessment plan must include, but is not limited to, the following:

REMS Assessment Plan

1. Number of prescribers enrolled (cumulative)
2. Number of new prescribers enrolled during reporting period
3. Number of prescribers ordering Mifeprex during reporting period
4. Number of healthcare providers who attempted to order Mifeprex who were not enrolled; describe actions taken (during reporting period and cumulative).
5. Number of women exposed to Mifeprex (during reporting period and cumulative)
6. Summary and analysis of any program deviations and corrective action taken
7. Based on the information reported, an assessment and analysis of whether the REMS is meeting its goals and whether modifications to the REMS are needed

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support any proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit any future supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.*

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 020687 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020687 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 020687/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020687/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate: (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call

(b) (6)

Sincerely,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

NDA 020687/S-020

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ENCLOSURES:

Content of Labeling

REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

03/29/2016

EXHIBIT 24

2000 MIFEPREX™ Label

**MIFEPREX™ (mifepristone) Tablets, 200 mg
For Oral Administration Only**

If Mifeprex* results in incomplete abortion, surgical intervention may be necessary. Prescribers should determine in advance whether they will provide such care themselves or through other providers. Prescribers should also give patients clear instructions on whom to call and what to do in the event of an emergency following administration of Mifeprex.

Prescribers should make sure that patients receive and have an opportunity to discuss the Medication Guide and the PATIENT AGREEMENT.

DESCRIPTION

Mifeprex tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical and biconvex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11β-[*p*-(Dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is C₂₉H₃₅NO₂. Its structural formula is:

The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 191-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

* Mifeprex is a trademark of Danco Laboratories, LLC.

CLINICAL PHARMACOLOGY

Pharmacodynamic Activity

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit and monkey), the compound inhibits the activity of endogenous or exogenous progesterone. The termination of pregnancy results.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women. During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins.

Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotrophic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

Pharmacokinetics and Metabolism

Absorption

Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 mg/l occurring approximately 90 minutes after ingestion. The absolute bioavailability of a 20 mg oral dose is 69%.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin and α_1 -acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance. Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11 β ; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum levels are undetectable by 11 days.

Special Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

Clinical Studies

Safety and efficacy data from the U.S. clinical trials and from two French trials of mifepristone are reported below. The U.S. trials provide safety data on 859 women and efficacy data on 827 women with gestation durations of 49 days or less (dated from the first day of the last menstrual period). In the two French clinical trials, safety evaluable data are available for 1800 women, while efficacy information is available for 1681 of these women. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure, for the U.S. and French studies appear in Table 1.

In the U.S. trials, 92.1% of the 827 subjects had a complete medical abortion, as shown in Table 1. In 52 women (6.3%) expulsion occurred within two days, and resulted from the action of mifepristone (600 mg) alone, unaided by misoprostol, an analog of prostaglandin E₂. All other women without an apparent expulsion took a 400 μ g dose of misoprostol two days after taking mifepristone. Many women (44.1%) in the U.S. trials expelled the products of conception within four hours after taking misoprostol and 62.8% experienced expulsion within 24 hours after the misoprostol administration. There were 65 women (7.9%) who received surgical interventions: 13 (1.6%) were medically indicated interventions during the study period, mostly for excessive bleeding; five (0.6%) interventions occurred at the patient's request; 39 women (4.7%) had incomplete abortions at the end of the study protocol; and eight (1.0%) had ongoing pregnancies at the end of the study protocol.

Women who participated in the U.S. trials reflect the racial and ethnic composition of American women. The majority of women (71.4%) were Caucasian, while 11.3% were African American, 10.9% were East Asian, and 4.7% were Hispanic. A small percentage (1.7%) belonged to other racial or ethnic groups. Women aged 18 to 45 were enrolled in the trials. Nearly two-thirds (66.0%) of the women were under 30 years old with a mean age of 27 years.

In the French trials, complete medical abortion occurred in 95.5% of the 1681 subjects, as shown in Table 1. In 89 women (5.3%), complete abortion occurred within two days of taking mifepristone (600 mg). About half of the women (50.3%) in the French trials expelled the products of conception during the first four hours immediately following administration of misoprostol and 72.3% experienced expulsion within 24 hours after taking misoprostol. In total, 4.5% of women in the French trials ultimately received surgical intervention for excessive bleeding, incomplete abortions, or ongoing pregnancies at the end of the protocol.

Table 1

**Outcome Following
Treatment with Mifepristone and Misoprostol in the U.S. and French Trials**

	<u>U.S. Trials</u>		<u>French Trials</u>	
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
Complete medical abortion	762	92.1	1605	95.5
<u>Timing of expulsion</u>				
Before second visit	52	(6.3)	89	(5.3)
During second visit				
– less than 4 hrs after misoprostol	365	(44.1)	846	(50.3)
After second visit				
– greater than 4 hrs but less than 24 hrs after misoprostol	155	(18.7)	370	(22.0)
– greater than 24 hrs after misoprostol	68	(8.2)	145	(8.6)
Time of expulsion unknown	122	(14.8)	155	(9.2)
Surgical intervention	65	7.9	76	4.5
<u>Reason for surgery</u>				
Medically necessary interventions during the study period	13	(1.6)	NA	(NA)
Patient request	5	(0.6)	NA	(NA)
Treatment of bleeding during study	NA	(NA)	6	(0.3)
Incomplete expulsion at study end	39	(4.7)	48	(2.9)
Ongoing pregnancy at study end	8	(1.0)	22	(1.3)
Total	827	100	1681	100

Note: Mifepristone 600 mg oral was administered on Day 1, misoprostol 400 µg oral was given on Day 3 (second visit).

INDICATION AND USAGE

Mifeprex is indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy. For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period in a presumed 28 day cycle with ovulation occurring at mid-cycle. The duration of pregnancy may be determined from menstrual history and by clinical examination. Ultrasonographic scan should be used if the duration of pregnancy is uncertain, or if ectopic pregnancy is suspected.

Any intrauterine device ("IUD") should be removed before treatment with Mifeprex begins.

Patients taking Mifeprex must take 400 µg of misoprostol two days after taking mifepristone unless a complete abortion has already been confirmed before that time (see DOSAGE AND ADMINISTRATION).

Pregnancy termination by surgery is recommended in cases when Mifeprex and misoprostol fail to cause termination of intrauterine pregnancy (see PRECAUTIONS).

CONTRAINDICATIONS

Administration of Mifeprex and misoprostol for the termination of pregnancy (the "treatment procedure") is contraindicated in patients with any one of the following conditions:

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy);
- IUD in place (see INDICATION AND USAGE);
- Chronic adrenal failure;
- Concurrent long-term corticosteroid therapy;
- History of allergy to mifepristone, misoprostol or other prostaglandin;
- Hemorrhagic disorders or concurrent anticoagulant therapy;
- Inherited porphyrias.

Because it is important to have access to appropriate medical care if an emergency develops, the treatment procedure is contraindicated if a patient does not have adequate access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions, and emergency resuscitation during the period from the first visit until discharged by the administering physician.

Mifeprex also should not be used by any patient who may be unable to understand the effects of the treatment procedure or to comply with its regimen. Patients should be instructed to review the Medication Guide and the PATIENT AGREEMENT provided with Mifeprex carefully and should be given a copy of the product label for their review.

Patients should discuss their understanding of these materials with their health care providers, and retain the Medication Guide for later reference (see PRECAUTIONS).

WARNINGS

(see CONTRAINDICATIONS)

1. Bleeding

Vaginal bleeding occurs in almost all patients during the treatment procedure. According to data from the U.S. and French trials, women should expect to experience bleeding or spotting for an average of nine to 16 days, while up to 8% of all subjects may experience some type of bleeding for 30 days or more. Bleeding was reported to last for 69 days in one patient in the French trials. In general the duration of bleeding and spotting increased as the duration of the pregnancy increased.

In some cases, excessive bleeding may require treatment by vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions. In the U.S. trials, 4.8% of subjects received administration of uterotonic medications and nine women (1.0%) received intravenous fluids. Vasoconstrictor drugs were used in 4.3% of all subjects in the French trials, and in 5.5% of women there was a decrease in hemoglobin of more than 2 g/dL. Blood transfusions were administered in one of 859 subjects in the U.S. trials and in two of 1800 subjects in the French trials. Since heavy bleeding requiring curettage occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

2. Confirmation of Pregnancy Termination

Patients should be scheduled for and return for a follow-up visit at approximately 14 days after administration of mifepristone to confirm that the pregnancy is completely terminated and to assess the degree of bleeding. Vaginal bleeding is not evidence of the termination of pregnancy. Termination can be confirmed by clinical examination or ultrasonographic scan. Lack of bleeding following treatment, however, usually indicates failure. Medical abortion failures should be managed with surgical termination.

PRECAUTIONS

General

Mifeprex is available only in single dose packaging. Administration must be under the supervision of a qualified physician (see DOSAGE AND ADMINISTRATION).

The use of Mifeprex is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

There are no data on the safety and efficacy of mifepristone in women with chronic medical conditions such as cardiovascular, hypertensive, hepatic, respiratory or renal

disease; insulin-dependent diabetes mellitus; severe anemia or heavy smoking. Women who are more than 35 years of age and who also smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone.

Although there is no clinical evidence, the effectiveness of Mifeprex may be lower if misoprostol is administered more than two days after mifepristone administration.

Information for Patients

Patients should be fully advised of the treatment procedure and its effects. Patients should be given a copy of the Medication Guide and the PATIENT AGREEMENT. (Additional copies of the Medication Guide and the PATIENT AGREEMENT are available by contacting Danco Laboratories at 1-877-4 Early Option) (1-877-432-7596). Patients should be advised to review both the Medication Guide and the PATIENT AGREEMENT, and should be given the opportunity to discuss them and obtain answers to any questions they may have. Each patient must understand:

- the necessity of completing the treatment schedule, including a follow-up visit approximately 14 days after taking Mifeprex;
- that vaginal bleeding and uterine cramping probably will occur;
- that prolonged or heavy vaginal bleeding is not proof of a complete expulsion;
- that if the treatment fails, there is a risk of fetal malformation;
- that medical abortion treatment failures are managed by surgical termination; and
- the steps to take in an emergency situation, including precise instructions and a telephone number that she can call if she has any problems or concerns.

Another pregnancy can occur following termination of pregnancy and before resumption of normal menses. Contraception can be initiated as soon as the termination of the pregnancy has been confirmed, or before the woman resumes sexual intercourse.

Patient information is included with each package of Mifeprex (see Medication Guide).

Laboratory Tests

Clinical examination is necessary to confirm the complete termination of pregnancy after the treatment procedure. Changes in quantitative human Chorionic Gonadotropin (hCG) levels will not be decisive until at least 10 days after the administration of Mifeprex. A continuing pregnancy can be confirmed by ultrasonographic scan.

The existence of debris in the uterus following the treatment procedure will not necessarily require surgery for its removal.

Decreases in hemoglobin concentration, hematocrit and red blood cell count occur in some women who bleed heavily. Hemoglobin decreases of more than 2 g/dL occurred in 5.5% of subjects during the French clinical trials of mifepristone and misoprostol.

Clinically significant changes in serum enzyme (serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, gamma-glutamyltransferase (GT)) activities were rarely reported.

Drug Interactions

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on in vitro inhibition information, coadministration of mifepristone may lead to an increase in serum levels of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range, including some agents used during general anesthesia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed. Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pombe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

The pharmacological activity of mifepristone disrupts the estrus cycle of animals, precluding studies designed to assess effects on fertility during drug administration. Three studies have been performed in rats to determine whether there were residual effects on reproductive function after termination of the drug exposure.

In rats, administration of the lowest oral dose of 0.3 mg/kg/day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effect on reproductive performance was observed. In a neonatal exposure study in rats, the administration of a subcutaneous dose of mifepristone up to 100 mg/kg on the first day after birth had no adverse effect on future reproductive function in males or females. The onset of puberty was observed to be slightly premature in female rats neonatally exposed to mifepristone. In a separate study in rats, oviduct and ovary malformations in female rats, delayed male puberty,

deficient male sexual behavior, reduced testicular size, and lowered ejaculation frequency were noted after exposure to mifepristone (1 mg every other day) as neonates.

Pregnancy

Mifepristone is indicated for use in the termination of pregnancy (through 49 days' pregnancy) and has no other approved indication for use during pregnancy.

Teratogenic Effects

Human Data

Over 620,000 women in Europe have taken mifepristone in combination with a prostaglandin to terminate pregnancy. Among these 620,000 women, about 415,000 have received mifepristone together with misoprostol. As of May 2000 a total of 82 cases have been reported in which women with on-going pregnancies after using mifepristone alone or mifepristone followed by misoprostol declined to have a surgical procedure at that time. These cases are summarized in Table 2.

Table 2

Reported Cases (as of May 2000) of On-going Pregnancies Not Terminated by Surgical

Abortion at the End of Treatment with Mifepristone Alone or with Mifepristone-Misoprostol

	Mifepristone Alone	Mifepristone- Misoprostol	Total
Subsequently had surgical abortion	3	7	10
<i>No abnormalities detected</i>	<i>2</i>	<i>7</i>	<i>9</i>
<i>Abnormalities detected</i> <i>(sirenomelia, cleft palate)</i>	<i>1</i>	<i>0</i>	<i>1</i>
Subsequently resulted in live birth	13	13	26
<i>No abnormalities detected at birth</i>	<i>13</i>	<i>13</i>	<i>26</i>
<i>Abnormalities detected at birth</i>	<i>0</i>	<i>0</i>	<i>0</i>
Other/Unknown	26	20	46
Total	42	40	82

Several reports in the literature indicate that prostaglandins, including misoprostol, may have teratogenic effects in human beings. Skull defects, cranial nerve palsies, delayed growth and psychomotor development, facial malformation and limb defects have all been reported after exposure during the first trimester.

Animal Data

Teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure level based on body surface area) were carried out. Because of the antiprogestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from decreased progesterone levels.

Nonteratogenic Effects

The indication for use of Mifeprex in conjunction with misoprostol is for the termination of pregnancy through 49 days' duration of pregnancy (as dated from the first day of the last menstrual period). These drugs together disrupt pregnancy by causing decidual necrosis, myometrial contractions and cervical softening, leading to the expulsion of the products of conception.

Nursing Mothers

It is not known whether mifepristone is excreted in human milk. Many hormones with a similar chemical structure, however, are excreted in breast milk. Since the effects of mifepristone on infants are unknown, breast-feeding women should consult with their health care provider to decide if they should discard their breast milk for a few days following administration of the medications.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The treatment procedure is designed to induce the vaginal bleeding and uterine cramping necessary to produce an abortion. Nearly all of the women who receive Mifeprex and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction. About 90% of patients report adverse reactions following administration of misoprostol on day three of the treatment procedure. Those adverse events that occurred with a frequency greater than 1% in the U.S. and French trials are shown in Table 3.

Bleeding and cramping are expected consequences of the action of Mifeprex as used in the treatment procedure. Following administration of mifepristone and misoprostol in the French clinical studies, 80 to 90% of women reported bleeding more heavily than they do during a heavy menstrual period (see WARNINGS, Bleeding for additional information). Women also typically experience abdominal pain, including uterine cramping. Other commonly reported side effects were nausea, vomiting and diarrhea. Pelvic pain, fainting, headache, dizziness, and asthenia occurred rarely. Some adverse reactions reported during the four hours following administration of misoprostol were judged by women as being more severe than others: the percentage of women who considered any particular adverse event as severe ranged from 2 to 35% in the U.S. and French trials. After the third day of the treatment procedure, the number of reports of adverse reactions declined progressively in the French trials, so that by day 14, reports were rare except for reports of bleeding and spotting.

Table 3**Type of Reported Adverse Events Following Administration of
Mifepristone and Misoprostol in the U.S. and French Trials* (percentages)**

	<u>U.S. Trials</u>	<u>French Trials</u>
Abdominal Pain (cramping)	96	NA
Uterine cramping	NA	83
Nausea	61	43
Headache	31	2
Vomiting	26	18
Diarrhea	20	12
Dizziness	12	1
Fatigue	10	NA
Back pain	9	NA
Uterine hemorrhage	5	NA
Fever	4	NA
Viral infections	4	NA
Vaginitis	3	NA
Rigors (chills/shaking)	3	NA
Dyspepsia	3	NA
Insomnia	3	NA
Asthenia	2	1
Leg pain	2	NA
Anxiety	2	NA
Anemia	2	NA
Leukorrhea	2	NA
Sinusitis	2	NA
Syncope	1	NA
Decrease in hemoglobin greater than 2 g/dL	NA	6
Pelvic pain	NA	2
Fainting	NA	2

* Only adverse reactions with incidence >1% are included.

OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than threefold that recommended for termination of pregnancy. If a patient ingests a massive overdose, she should be observed closely for signs of adrenal failure.

The oral acute lethal dose of mifepristone in the mouse, rat and dog is greater than 1000 mg/kg (about 100 times the human dose recommended for termination of pregnancy).

DOSAGE AND ADMINISTRATION

Treatment with Mifeprex and misoprostol for the termination of pregnancy requires three office visits by the patient. Mifeprex should be prescribed only by physicians who have read and understood the prescribing information. Mifeprex may be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies. Physicians must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

Day One: Mifeprex Administration

Patients must read the Medication Guide and read and sign the PATIENT AGREEMENT before Mifeprex is administered.

Three 200 mg tablets (600 mg) of Mifeprex are taken in a single oral dose.

Day Three: Misoprostol Administration

The patient returns to the healthcare provider two days after ingesting Mifeprex. Unless abortion has occurred and has been confirmed by clinical examination or ultrasonographic scan, the patient takes two 200 µg tablets (400 µg) of misoprostol orally.

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms (see ADVERSE REACTIONS). The patient should be given instructions on what to do if significant discomfort, excessive bleeding or other adverse reactions occur and should be given a phone number to call if she has questions following the administration of the misoprostol. In addition, the name and phone number of the physician who will be handling emergencies should be provided to the patient.

Day 14: Post-Treatment Examination

Patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex. This visit is very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred.

According to data from the U.S. and French studies, women should expect to experience bleeding or spotting for an average of nine to 16 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at this visit, however, could indicate an incomplete abortion.

Patients who have an ongoing pregnancy at this visit have a risk of fetal malformation resulting from the treatment. Surgical termination is recommended to manage medical abortion treatment failures (see PRECAUTIONS, Pregnancy).

Adverse events, such as hospitalization, blood transfusion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol must be reported to Danco Laboratories. Please provide a brief clinical and administrative synopsis of any such adverse events in writing to:

Medical Director
Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4-Early Option (1-877-432-7596)

For immediate consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

HOW SUPPLIED

Mifeprex will be supplied only to licensed physicians who sign and return a Prescriber's Agreement. Distribution of Mifeprex will be subject to specific requirements imposed by the distributor, including procedures for storage, dosage tracking, damaged product returns and other matters. Mifeprex is a prescription drug, although it will not be available to the public through licensed pharmacies.

Mifeprex is supplied as light yellow, cylindrical, bi-convex tablets imprinted on one side with "MF." Each tablet contains 200 mg of mifepristone. Tablets are packaged in single dose blister packets containing three tablets and are supplied in individual cartons (National Drug Code 6487500103).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Manufactured for:

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

EXHIBIT 25

2023 Mifeprex Prescribing and Label Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MIFEPREX safely and effectively. See full prescribing information for MIFEPREX.

MIFEPREX* (mifepristone) tablets, for oral use
Initial U.S. Approval: 2000

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

See full prescribing information for complete boxed warning.

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use.

- Atypical Presentation of Infection. Patients with serious bacterial infections and sepsis can present without fever, bacteremia or significant findings on pelvic examination. A high index of suspicion is needed to rule out serious infection and sepsis. (5.1)
- Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. (5.2)

MIFEPREX is only available through a restricted program called the mifepristone REMS Program (5.3).

Before prescribing MIFEPREX, inform the patient about these risks. Ensure the patient knows whom to call and what to do if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort or general malaise for more than 24 hours after taking misoprostol.

INDICATIONS AND USAGE

MIFEPREX is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. (1)

DOSAGE AND ADMINISTRATION

- 200 mg MIFEPREX on Day 1, followed 24–48 hours after MIFEPREX dosing by 800 mcg buccal misoprostol. (2.1)
- Instruct the patient what to do if significant adverse reactions occur. (2.2)
- Follow-up is needed to confirm complete termination of pregnancy. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card (3)

CONTRAINDICATIONS

- Confirmed/suspected ectopic pregnancy or undiagnosed adnexal mass (4)
- Chronic adrenal failure (4)
- Concurrent long-term corticosteroid therapy (4)
- History of allergy to mifepristone, misoprostol, or other prostaglandins (4)
- Hemorrhagic disorders or concurrent anticoagulant therapy (4)
- Inherited porphyria (4)
- Intrauterine device (IUD) in place (4)

WARNINGS AND PRECAUTIONS

- Ectopic pregnancy: Exclude before treatment. (5.4)
- Rhesus immunization: Prevention needed as for surgical abortion. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (>15%) are nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Danco Laboratories, LLC at 1-877-432-7596 or medicaldirector@earlyoptionpill.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP3A4 inducers can lower mifepristone concentrations. (7.1)
- CYP3A4 inhibitors can increase mifepristone concentrations. Use with caution. (7.2)
- CYP3A4 substrate concentrations can be increased. Caution with coadministration of substrates with narrow therapeutic margin. (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Risk of fetal malformations in ongoing pregnancy if not terminated is unknown. (8.1)

See 17 for PATIENT COUNSELING INFORMATION, Medication Guide.

Revised: 01/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use. No causal relationship between the use of MIFEPREX and misoprostol and these events has been established.

- **Atypical Presentation of Infection.** Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis [see *Warnings and Precautions* (5.1)].
- **Bleeding.** Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding [see *Warnings and Precautions* (5.2)].

Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the mifepristone REMS Program [see *Warnings and Precautions* (5.3)].

Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting, or diarrhea) for more than 24 hours after taking misoprostol.

1 INDICATIONS AND USAGE

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Regimen

For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period. The duration of pregnancy may be determined from menstrual history and clinical examination. Assess the pregnancy by ultrasonographic scan if the duration of pregnancy is uncertain or if ectopic pregnancy is suspected.

Remove any intrauterine device ("IUD") before treatment with MIFEPREX begins [see *Contraindications* (4)].

The dosing regimen for MIFEPREX and misoprostol is:

- MIFEPREX 200 mg orally + misoprostol 800 mcg buccally
 - *Day One: MIFEPREX Administration*
One 200 mg tablet of MIFEPREX is taken in a single oral dose.
 - *Day Two or Three: Misoprostol Administration* (minimum 24-hour interval between MIFEPREX and misoprostol)
Four 200 mcg tablets (total dose 800 mcg) of misoprostol are taken by the buccal route.

Tell the patient to place two 200 mcg misoprostol tablets in each cheek pouch (the area between the cheek and gums) for 30 minutes and then swallow any remnants with water or another liquid (see Figure 1).

Figure 1



2 pills between cheek and gum on left side + 2 pills between cheek and gum on right side

Patients taking MIFEPREX must take misoprostol within 24 to 48 hours after taking MIFEPREX. The effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours or more than 48 hours after mifepristone administration.

Because most women will expel the pregnancy within 2 to 24 hours of taking misoprostol [see *Clinical Studies* (14)], discuss with the patient an appropriate location for them to be when taking the misoprostol, taking into account that expulsion could begin within 2 hours of administration.

2.2 Patient Management Following Misoprostol Administration

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms [see *Adverse Reactions* (6)].

Give the patient:

- Instructions on what to do if significant discomfort, excessive vaginal bleeding or other adverse reactions occur
- A phone number to call if the patient has questions following the administration of the misoprostol
- The name and phone number of the healthcare provider who will be handling emergencies.

2.3 Post-treatment Assessment: Day 7 to 14

Patients should follow-up with their healthcare provider approximately 7 to 14 days after the administration of MIFEPREX. This assessment is very important to confirm that complete termination of pregnancy has occurred and to evaluate the degree of bleeding. Termination can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan. Lack of bleeding following treatment usually indicates failure; however, prolonged or heavy bleeding is not proof of a complete abortion.

The existence of debris in the uterus (e.g., if seen on ultrasonography) following the treatment procedure will not necessarily require surgery for its removal.

Patients should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at the time of follow-up, however, could indicate an incomplete abortion.

If complete expulsion has not occurred, but the pregnancy is not ongoing, patients may be treated with another dose of misoprostol 800 mcg buccally. There have been rare reports of uterine rupture in women who took MIFEPREX and misoprostol, including women with prior uterine rupture or uterine scar and women who received multiple doses of misoprostol within 24 hours. Patients who choose to use a repeat dose of misoprostol should have a follow-up visit with their healthcare provider in approximately 7 days to assess for complete termination.

Surgical evacuation is recommended to manage ongoing pregnancies after medical abortion [see *Use in Specific Populations (8.1)*]. Advise the patient whether you will provide such care or will refer them to another provider as part of counseling prior to prescribing MIFEPREX.

2.4 Contact for Consultation

For consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

3 DOSAGE FORMS AND STRENGTHS

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card. MIFEPREX tablets are light yellow, cylindrical, and bi-convex tablets, approximately 11 mm in diameter and imprinted on one side with "MF."

4 CONTRAINDICATIONS

- Administration of MIFEPREX and misoprostol for the termination of pregnancy (the "treatment procedure") is contraindicated in patients with any of the following conditions:
 - Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy) [see *Warnings and Precautions (5.4)*]
 - Chronic adrenal failure (risk of acute adrenal insufficiency)
 - Concurrent long-term corticosteroid therapy (risk of acute adrenal insufficiency)
 - History of allergy to mifepristone, misoprostol, or other prostaglandins (allergic reactions including anaphylaxis, angioedema, rash, hives, and itching have been reported [see *Adverse Reactions (6.2)*])
 - Hemorrhagic disorders or concurrent anticoagulant therapy (risk of heavy bleeding)

- Inherited porphyrias (risk of worsening or of precipitation of attacks)
- Use of MIFEPREX and misoprostol for termination of intrauterine pregnancy is contraindicated in patients with an intrauterine device ("IUD") in place (the IUD might interfere with pregnancy termination). If the IUD is removed, MIFEPREX may be used.

5 WARNINGS AND PRECAUTIONS

5.1 Infection and Sepsis

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX [see *Boxed Warning*]. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting, or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

5.2 Uterine Bleeding

Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications, and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion [see *Boxed Warning*].

Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.

Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in patients who bleed heavily.

Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfusions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to ≤ 0.1% of subjects. Because heavy bleeding requiring surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

5.3 Mifepristone REMS Program

MIFEPREX is available only through a restricted program under a REMS called the mifepristone REMS Program, because of the risks of serious complications [see *Warnings and Precautions* (5.1, 5.2)].

Notable requirements of the mifepristone REMS Program include the following:

- Prescribers must be certified with the program by completing the Prescriber Agreement Form.
- Patients must sign a Patient Agreement Form.
- MIFEPREX must only be dispensed to patients by or under the supervision of a certified prescriber, or by certified pharmacies on prescriptions issued by certified prescribers.

Further information is available at 1-877-4 Early Option (1-877-432-7596).

5.4 Ectopic Pregnancy

MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies [see *Contraindications* (4)]. Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.

Patients who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

5.5 Rhesus Immunization

The use of MIFEPREX is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Infection and sepsis [see *Warnings and Precautions* (5.1)]
- Uterine bleeding [see *Warnings and Precautions* (5.2)]

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Information presented on common adverse reactions relies solely on data from U.S. studies, because rates reported in non-U.S. studies were markedly lower and are not likely generalizable to the U.S. population. In three U.S. clinical studies totaling 1,248 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally, women reported adverse reactions in diaries and in interviews at the follow-up visit. These studies enrolled generally healthy women of reproductive age without contraindications to mifepristone or misoprostol use according to the MIFEPREX product label. Gestational age was assessed prior to study enrollment using the date of the woman's last menstrual period, clinical evaluation, and/or ultrasound examination.

About 85% of patients report at least one adverse reaction following administration of MIFEPREX and misoprostol, and many can be expected to report more than one such reaction. The most commonly reported adverse reactions (>15%) were nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness (see Table 1). The frequency of adverse reactions varies between studies and may be dependent on many factors, including the patient population and gestational age.

Abdominal pain/cramping is expected in all medical abortion patients and its incidence is not reported in clinical studies. Treatment with MIFEPREX and misoprostol is designed to induce uterine bleeding and cramping to cause termination of an intrauterine pregnancy. Uterine bleeding and cramping are expected consequences of the action of MIFEPREX and misoprostol as used in the treatment procedure. Most patients can expect bleeding more heavily than they do during a heavy menstrual period [see *Warnings and Precautions* (5.2)].

Table 1 lists the adverse reactions reported in U.S. clinical studies with incidence >15% of women.

Table 1
Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. Clinical Studies

Adverse Reaction	# U.S. studies	Number of Evaluable Women	Range of frequency (%)	Upper Gestational Age of Studies Reporting Outcome
Nausea	3	1,248	51-75%	70 days
Weakness	2	630	55-58%	63 days
Fever/chills	1	414	48%	63 days
Vomiting	3	1,248	37-48%	70 days
Headache	2	630	41-44%	63 days
Diarrhea	3	1,248	18-43%	70 days
Dizziness	2	630	39-41%	63 days

One study provided gestational-age stratified adverse reaction rates for women who were 57-63 and 64-70 days; there was little difference in frequency of the reported common adverse reactions by gestational age.

Information on serious adverse reactions was reported in six U.S. and four non-U.S. clinical studies, totaling 30,966 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally. Serious adverse reaction rates were similar between U.S. and non-U.S. studies, so rates from both U.S. and non-U.S. studies are presented. In the U.S. studies, one studied women through 56 days gestation, four through 63 days gestation, and one through 70 days gestation, while in the non-U.S. studies, two studied women through 63 days gestation, and two through 70 days gestation. Serious adverse reactions were reported in <0.5% of women. Information from the U.S. and non-U.S. studies is presented in Table 2.

Table 2
Serious Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. and Non-U.S. Clinical Studies

Adverse Reaction	U.S.			Non-U.S.		
	# of studies	Number of Evaluable Women	Range of frequency (%)	# of studies	Number of Evaluable Women	Range of frequency (%)
Transfusion	4	17,774	0.03-0.5%	3	12,134	0-0.1%
Sepsis	1	629	0.2%	1	11,155	<0.01%*
ER visit	2	1,043	2.9-4.6%	1	95	0
Hospitalization Related to Medical Abortion	3	14,339	0.04-0.6%	3	1,286	0-0.7%
Infection without sepsis	1	216	0	1	11,155	0.2%
Hemorrhage	NR	NR	NR	1	11,155	0.1%

NR= Not reported

* This outcome represents a single patient who experienced death related to sepsis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of MIFEPREX and misoprostol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations: post-abortion infection (including endometritis, endomyometritis, parametritis, pelvic infection, pelvic inflammatory disease, salpingitis)

Blood and the lymphatic system disorders: anemia

Immune system disorders: allergic reaction (including anaphylaxis, angioedema, hives, rash, itching)

Psychiatric disorders: anxiety

Cardiac disorders: tachycardia (including racing pulse, heart palpitations, heart pounding)

Vascular disorders: syncope, fainting, loss of consciousness, hypotension (including orthostatic), light-headedness

Respiratory, thoracic and mediastinal disorders: shortness of breath

Gastrointestinal disorders: dyspepsia

Musculoskeletal, connective tissue and bone disorders: back pain, leg pain

Reproductive system and breast disorders: uterine rupture, ruptured ectopic pregnancy, hematometra, leukorrhea

General disorders and administration site conditions: pain

7 DRUG INTERACTIONS

7.1 Drugs that May Reduce MIFEPREX Exposure (Effect of CYP 3A4 Inducers on MIFEPREX)

CYP450 3A4 is primarily responsible for the metabolism of mifepristone. CYP3A4 inducers such as rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (such as phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum concentrations of mifepristone). Whether this action has an impact on the efficacy of the dose

regimen is unknown. Refer to the follow-up assessment [see *Dosage and Administration* (2.3)] to verify that treatment has been successful.

7.2 Drugs that May Increase MIFEPREX Exposure (Effect of CYP 3A4 Inhibitors on MIFEPREX)

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum concentrations of mifepristone). MIFEPREX should be used with caution in patients currently or recently treated with CYP 3A4 inhibitors.

7.3 Effects of MIFEPREX on Other Drugs (Effect of MIFEPREX on CYP 3A4 Substrates)

Based on *in vitro* inhibition information, coadministration of mifepristone may lead to an increase in serum concentrations of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Risks to pregnant patients are discussed throughout the labeling.

Refer to misoprostol labeling for risks to pregnant patients with the use of misoprostol.

The risk of adverse developmental outcomes with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol is unknown; however, the process of a failed pregnancy termination could disrupt normal embryo-fetal development and result in adverse developmental effects. Birth defects have been reported with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol. In animal reproduction studies, increased fetal losses were observed in mice, rats, and rabbits and skull deformities were observed in rabbits with administration of mifepristone at doses lower than the human exposure level based on body surface area.

Data

Animal Data

In teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure based on body surface area), because of the antiprogesterational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from inhibition of progesterone action.

8.2 Lactation

MIFEPREX is present in human milk. Limited data demonstrate undetectable to low levels of the drug in human milk with the relative (weight-adjusted) infant dose 0.5% or less as compared to maternal dosing. There is no information on the effects of MIFEPREX in a regimen with

misoprostol in a breastfed infant or on milk production. Refer to misoprostol labeling for lactation information with the use of misoprostol. The developmental and health benefits of breast-feeding should be considered along with any potential adverse effects on the breast-fed child from MIFEPREX in a regimen with misoprostol.

8.4 Pediatric Use

Safety and efficacy of MIFEPREX have been established in pregnant females. Data from a clinical study of MIFEPREX that included a subset of 322 females under age 17 demonstrated a safety and efficacy profile similar to that observed in adults.

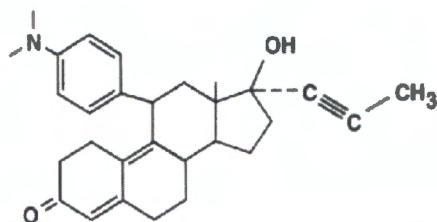
10 OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than 1800 mg (ninefold the recommended dose for medical abortion). If a patient ingests a massive overdose, the patient should be observed closely for signs of adrenal failure.

11 DESCRIPTION

MIFEPREX tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical, and bi-convex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11 β -[p-(Dimethylamino)phenyl]-17 β -hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is C₂₉H₃₅NO₂. Its structural formula is:



The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 192-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit, and monkey), the compound inhibits the activity of endogenous or exogenous progesterone, resulting in effects on the uterus and cervix that, when combined with misoprostol, result in termination of an intrauterine pregnancy.

During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity

of prostaglandins.

12.2 Pharmacodynamics

Use of MIFEPREX in a regimen with misoprostol disrupts pregnancy by causing decidual necrosis, myometrial contractions, and cervical softening, leading to the expulsion of the products of conception.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women.

Antiglucocorticoid and antiandrogenic activity: Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotrophic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

12.3 Pharmacokinetics

Mifepristone is rapidly absorbed after oral ingestion with non-linear pharmacokinetics for C_{max} after single oral doses of 200 mg and 600 mg in healthy subjects.

Absorption

The absolute bioavailability of a 20 mg mifepristone oral dose in females of childbearing age is 69%. Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 ± 1.0 mg/L occurring approximately 90 minutes after ingestion.

Following oral administration of a single dose of 200 mg in healthy men (n=8), mean C_{max} was 1.77 ± 0.7 mg/L occurring approximately 45 minutes after ingestion. Mean AUC_{0-∞} was 25.8 ± 6.2 mg*hr/L.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin, and α_1 -acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance.

Elimination

Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11β; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum concentrations are undetectable by 11 days.

Specific Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed.

Mutagenesis

Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pombe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

Impairment of Fertility

In rats, administration of 0.3 mg/kg mifepristone per day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effects on reproductive performance were observed.

14 CLINICAL STUDIES

Safety and efficacy data from clinical studies of mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally through 70 days gestation are reported below. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure based on 22 worldwide clinical studies (including 7 U.S. studies) appear in Table 3.

The demographics of women who participated in the U.S. clinical studies varied depending on study location and represent the racial and ethnic variety of American females. Females of all reproductive ages were represented, including females less than 18 and more than 40 years of age; most were 27 years or younger.

Table 3
Outcome Following Treatment with Mifepristone (oral) and Misoprostol (buccal)
Through 70 Days Gestation

	U.S. Trials	Non-U.S. Trials
N	16,794	18,425
Complete Medical Abortion	97.4%	96.2%
Surgical Intervention*	2.6%	3.8%
Ongoing Pregnancy**	0.7%	0.9%
* Reasons for surgical intervention include ongoing pregnancy, medical necessity, persistent or heavy bleeding after treatment, patient request, or incomplete expulsion.		
** Ongoing pregnancy is a subcategory of surgical intervention, indicating the percent of women who have surgical intervention due to an ongoing pregnancy.		

The results for clinical studies that reported outcomes, including failure rates for ongoing pregnancy, by gestational age are presented in Table 4.

Table 4
Outcome by Gestational Age Following Treatment with Mifepristone and
Misoprostol (buccal) for U.S. and Non-U.S. Clinical Studies

	≤49 days			50-56 days			57-63 days			64-70 days		
	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies
Complete medical abortion	12,046	98.1	10	3,941	96.8	7	2,294	94.7	9	479	92.7	4
Surgical intervention for ongoing pregnancy	10,272	0.3	6	3,788	0.8	6	2,211	2	8	453	3.1	3

One clinical study asked subjects through 70 days gestation to estimate when they expelled the pregnancy, with 70% providing data. Of these, 23-38% reported expulsion within 3 hours and over 90% within 24 hours of using misoprostol.

16 HOW SUPPLIED/STORAGE AND HANDLING

is only available through a restricted program called the Mifepristone REMS Program [see *Warnings and Precautions* (5.3)].

MIFEPREX is supplied as light yellow, cylindrical, and bi-convex tablets imprinted on one side with "MF." Each tablet contains 200 mg of mifepristone. One tablet is individually blistered on one blister card that is packaged in an individual package (National Drug Code 64875-001-01).

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide), included with each package of MIFEPREX. Additional copies of the Medication Guide are available by contacting Danco Laboratories at 1-877-4 Early Option (1-877-432-7596) or from www.earlyoptionpill.com.

Serious Infections and Bleeding

- Inform the patient that uterine bleeding and uterine cramping will occur [see *Warnings and Precautions* (5.2)].
- Advise the patient that serious and sometimes fatal infections and bleeding can occur very rarely [see *Warnings and Precautions* (5.1, 5.2)].
- MIFEPREX is only available through a restricted program called the Mifepristone REMS Program [see *Warnings and Precautions* (5.3)]. Under the mifepristone REMS Program:
 - Patients must sign a Patient Agreement Form.
 - MIFEPREX is only dispensed by or under the supervision of certified prescribers or by certified pharmacies on prescriptions issued by certified prescribers.

Provider Contacts and Actions in Case of Complications

- Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, or if the patient experiences complications including prolonged heavy bleeding, severe abdominal pain, or sustained fever [see *Boxed Warning*].
-

Compliance with Treatment Schedule and Follow-up Assessment

- Advise the patient that it is necessary to complete the treatment schedule, including a follow-up assessment approximately 7 to 14 days after taking MIFEPREX [see *Dosage and Administration* (2.3)].
- Explain that
 - prolonged heavy vaginal bleeding is not proof of a complete abortion,
 - if the treatment fails and the pregnancy continues, the risk of fetal malformation is unknown,
 - it is recommended that ongoing pregnancy be managed by surgical termination [see *Dosage and Administration* (2.3)]. Advise the patient whether you will provide such care or will refer them to another provider.

Subsequent Fertility

- Inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses.
- Inform the patient that contraception can be initiated as soon as pregnancy expulsion has been confirmed, or before resuming sexual intercourse.

MIFEPREX is a registered trademark of Danco Laboratories, LLC.

Manufactured for:
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01/2023

<p style="text-align: center;">MEDICATION GUIDE</p> <p style="text-align: center;">Mifeprex (MIF-eh-prex) (mifepristone tablets, for oral use)</p>
<p>Read this information carefully before taking Mifeprex and misoprostol. It will help you understand how the treatment works. This Medication Guide does not take the place of talking with your healthcare provider.</p>
<p>What is the most important information I should know about Mifeprex?</p> <p>What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Seeking medical attention as soon as possible is needed in these circumstances. Serious infection has resulted in death in a very small number of cases. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your healthcare provider. You can write down your healthcare provider's telephone number here _____.</p> <p>Be sure to contact your healthcare provider promptly if you have any of the following:</p> <ul style="list-style-type: none"> • Heavy Bleeding. Contact your healthcare provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C). • Abdominal Pain or "Feeling Sick." If you have abdominal pain or discomfort, or you are "feeling sick," including weakness, nausea, vomiting, or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your healthcare provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb). • Fever. In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your healthcare provider right away. Fever may be a symptom of a serious infection or another problem. <p>If you cannot reach your healthcare provider, go to the nearest hospital emergency room.</p> <p>What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy. In many cases, this surgical procedure can be done in the office/clinic. The chance of birth defects if the pregnancy is not ended is unknown.</p> <p>Talk with your healthcare provider. Before you take Mifeprex, you should read this Medication Guide and you and your healthcare provider should discuss the benefits and risks of your using Mifeprex.</p>

What is Mifeprex?

Mifeprex is used in a regimen with another prescription medicine called misoprostol, to end an early pregnancy. Early pregnancy means it is 70 days (10 weeks) or less since your last menstrual period began. Mifeprex is not approved for ending pregnancies that are further along. Mifeprex blocks a hormone needed for your pregnancy to continue. When you use Mifeprex on Day 1, you also need to take another medicine called misoprostol 24 to 48 hours after you take Mifeprex, to cause the pregnancy to be passed from your uterus.

The pregnancy is likely to be passed from your uterus within 2 to 24 hours after taking Mifeprex and misoprostol. When the pregnancy is passed from the uterus, you will have bleeding and cramping that will likely be heavier than your usual period. About 2 to 7 out of 100 women taking Mifeprex will need a surgical procedure because the pregnancy did not completely pass from the uterus or to stop bleeding.

Who should not take Mifeprex?

Some patients should not take Mifeprex. Do not take Mifeprex if you:

- Have a pregnancy that is more than 70 days (10 weeks). Your healthcare provider may do a clinical examination, an ultrasound examination, or other testing to determine how far along you are in pregnancy.
- Are using an IUD (intrauterine device or system). It must be taken out before you take Mifeprex.
- Have been told by your healthcare provider that you have a pregnancy outside the uterus (ectopic pregnancy).
- Have problems with your adrenal glands (chronic adrenal failure).
- Take a medicine to thin your blood.
- Have a bleeding problem.
- Have porphyria.
- Take certain steroid medicines.
- Are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Ask your healthcare provider if you are not sure about all your medical conditions before taking this medicine to find out if you can take Mifeprex.

What should I tell my healthcare provider before taking Mifeprex?

Before you take Mifeprex, tell your healthcare provider if you:

- cannot follow-up within approximately 7 to 14 days of your first visit
- are breastfeeding. Mifeprex can pass into your breast milk. The effect of the Mifeprex and misoprostol regimen on the breastfed infant or on milk production is unknown.
- are taking medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Mifeprex and certain other medicines may affect each other if they are used together. This can cause side effects.

How should I take Mifeprex?

- Mifeprex will be given to you by a healthcare provider or pharmacy.
- You and your healthcare provider will plan the most appropriate location for you to take the misoprostol, because it may cause bleeding, cramps, nausea, diarrhea, and other symptoms that usually begin within 2 to 24 hours after taking it.
- Most women will pass the pregnancy within 2 to 24 hours after taking the misoprostol tablets.

Follow the instruction below on how to take Mifeprex and misoprostol:

Mifeprex (1 tablet) orally + misoprostol (4 tablets) buccally

Day 1:

- Take 1 Mifeprex tablet by mouth.

24 to 48 hours after taking Mifeprex:

- Take 4 misoprostol tablets by placing 2 tablets in each cheek pouch (the area between your teeth and cheek - see Figure A) for 30 minutes and then swallow anything left over with a drink of water or another liquid.
- The medicines may not work as well if you take misoprostol sooner than 24 hours after Mifeprex or later than 48 hours after Mifeprex.
- Misoprostol often causes cramps, nausea, diarrhea, and other symptoms. Your healthcare provider may send you home with medicines for these symptoms.



Figure A (2 tablets between your left cheek and gum and 2 tablets between your right cheek and gum).

Follow-up Assessment at Day 7 to 14:

- This follow-up assessment is very important. You must follow-up with your healthcare provider about 7 to 14 days after you have taken Mifeprex to be sure you are well and that you have had bleeding and the pregnancy has passed from your uterus.
- Your healthcare provider will assess whether your pregnancy has passed from your uterus. If your pregnancy continues, the chance that there may be birth defects is unknown. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy.
- If your pregnancy has ended, but has not yet completely passed from your uterus, your provider will talk with you about other choices you have, including waiting, taking another dose of misoprostol, or having a surgical procedure to empty your uterus.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or over-the-counter medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your healthcare provider about them because they may interfere with the treatment. Ask your healthcare provider about what medicines you can take for pain and other side effects.

What are the possible side effects of Mifeprex and misoprostol?

Mifeprex may cause serious side effects. See “What is the most important information I should know about Mifeprex?”

Cramping and bleeding. Cramping and vaginal bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must follow-up with your healthcare provider approximately 7 to 14 days after taking Mifeprex. See “How should I take Mifeprex?” for more information on your follow-up assessment. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take 24 to 48 hours after Mifeprex. Bleeding or spotting can be expected for an average of 9 to 16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of passing the pregnancy.

The most common side effects of Mifeprex treatment include: nausea, weakness, fever/chills, vomiting, headache, diarrhea and dizziness. Your provider will tell you how to manage any pain or other side effects. These are not all the possible side effects of Mifeprex.

Call your healthcare provider for medical advice about any side effects that bother you or do not go away. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Mifeprex.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Mifeprex. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider for information about Mifeprex that is written for healthcare professionals.

For more information about Mifeprex, go to www.earlyoptionpill.com or call 1-877-4 Early Option (1-877-432-7596).

Manufactured for: *Danco Laboratories, LLC*
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This Medication Guide has been approved by the U.S. Food and Drug Administration. Approval
01/2023

EXHIBIT 26

**Chen, Mifepristone with Buccal Misoprostol for Medical
Abortion 126 Obstetrics & Gynecology 12 (Jul. 2015)**

Family Planning: Review

Mifepristone With Buccal Misoprostol for Medical Abortion

A Systematic Review

Melissa J. Chen, MD, MPH, and Mitchell D. Creinin, MD

OBJECTIVE: To summarize clinical outcomes and adverse effects of medical abortion regimens consisting of mifepristone followed by buccal misoprostol in pregnancies through 70 days of gestation.

DATA SOURCES: We used PubMed, ClinicalTrials.gov, and reference lists from published reports to identify relevant studies published between November 2005 and January 2015 using the search terms “mifepristone and medical abortion” and “buccal and misoprostol.”

METHODS OF STUDY SELECTION: Studies were included if they presented clinical outcomes of medical abortion using mifepristone and buccal misoprostol through 70 days of gestation. Studies with duplicate data were excluded.

TABULATION, INTEGRATION, AND RESULTS: We included 20 studies with a total of 33,846 women through 70 days of gestation. We abstracted efficacy and ongoing pregnancy rates as an overall rate and by gestational age in days in reference to completed weeks (eg, 49 days or less, 50–56 days, 57–63 days, 64–70 days) and adverse effects when reported. The overall efficacy of mifepristone followed by buccal misoprostol is 96.7% (95% confidence interval [CI] 96.5–96.8%) and the continuing pregnancy rate is 0.8% (95% CI 0.7–0.9%) in approximately 33,000 pregnancies through 63 days of gestation. Only 332 women with pregnancies between 64 and 70 days of gestation are reported in the literature with an overall efficacy of 93.1% (95% CI 89.6–95.5%) and a continuing pregnancy

rate of 2.9% (95% CI 1.4–5.7%). Currently available data suggest that regimens with a 24-hour time interval between mifepristone and buccal misoprostol administration are slightly less effective than those with a 24- to 48-hour interval. Rates of surgical evacuation for reasons other than ongoing pregnancy range from 1.8% to 4.2%. Severe adverse events like blood transfusion (0.03–0.6%) and hospitalization (0.04–0.9%) are uncommon.

CONCLUSION: Outpatient medical abortion regimens with mifepristone followed in 24–48 hours by buccal misoprostol are highly effective for pregnancy termination through 63 days of gestation. More data are needed to evaluate clinical outcomes with regimens containing mifepristone followed in 24 hours by buccal misoprostol and in pregnancies beyond 63 days of gestation.

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The use of medical abortion for pregnancy termination is increasing in the United States. In 2011, approximately 239,400 medical abortions were performed, which was a 20% increase from 2008.¹ The current U.S. Food and Drug Administration (FDA)-approved regimen for medical abortion consists of 600 mg mifepristone orally followed in 48 hours by 400 micrograms misoprostol orally in pregnancies up to 49 days based on initial clinical trials.² Studies since FDA approval in 2000 have accumulated evidence demonstrating increased efficacy in regimens with a lower dose of mifepristone and a higher dose of misoprostol, even in pregnancies past 49 days of gestation. The transition from oral to alternative routes of administration, including vaginal, buccal, and sublingual, is associated with increased efficacy and fewer side effects.^{3,4} National evidence-based clinical guidelines in the United States, the United Kingdom, and other countries clearly identify that regimens other than the current FDA-approved regimen are superior based on higher efficacy and fewer adverse effects.^{3,5}

See related editorial on page 3.

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Dr. Creinin is a consultant for Danco. The other author did not report any potential conflicts of interest.

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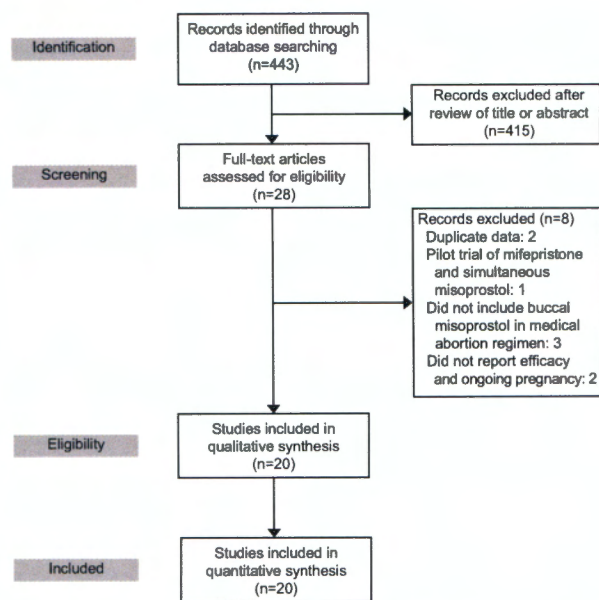


Fig. 1. Flow diagram of selected studies for systematic review.

Chen. Medical Abortion With Buccal Misoprostol. *Obstet Gynecol* 2015.

Vaginal misoprostol administration was routinely used in the United States until reports of severe infection with *Clostridium sordellii* after medical abortion surfaced,⁶ prompting a reevaluation of vaginal misoprostol and a search for alternative routes of misoprostol administration. Although the use of vaginal misoprostol was ultimately not the cause of these infections, continued safety evaluations from Planned Parenthood Federation of

America showed that severe infection, albeit a rare complication, decreased after changing to a buccal misoprostol regimen in addition to screening for sexually transmitted infections or providing routine preventive antibiotic coverage as part of the medical abortion.⁷

With buccal administration, misoprostol is held in the buccal pouch between the teeth and gums for 30 minutes before swallowing any remaining tablets. Buccal misoprostol is slowly absorbed, unlike oral misoprostol, which is rapidly absorbed and undergoes extensive first-pass metabolism. After a dose of oral misoprostol, plasma misoprostol acid levels peak quickly at 30 minutes and decrease rapidly by 120 minutes.⁸ In contrast, after buccal administration, plasma misoprostol acid levels rise gradually to peak concentration after a median time of 75 minutes and fall slowly over several hours.^{8–10}

Within the last 10 years, buccal misoprostol use with mifepristone for medical abortion has become commonplace. However, the published literature did not contain abundant information about medical abortion outcomes with buccal misoprostol until recently. In this systematic review, we summarize clinical outcomes and adverse effects of medical abortion regimens consisting of mifepristone followed by buccal misoprostol in pregnancies through 70 days of gestation.

SOURCES

We searched PubMed (<http://www.ncbi.nlm.nih.gov/>) for all relevant studies published from November 1, 2005, through January 31, 2015,

Table 1. Efficacy and Ongoing Pregnancy Rates With Mifepristone and Buccal Misoprostol for Medical Abortion Through 70 Days of Gestation

	Successful Abortion			Ongoing Pregnancy		
	No. in Analysis	No. Successful	% (95% CI)	No. in Analysis	No. of Ongoing Pregnancies	% (95% CI)
Overall						
Through 63 d of gestation	33,514	32,394	96.7 (96.5–96.8)	32,479	252	0.8 (0.7–0.9)
Through 70 d of gestation	33,846	32,703	96.6 (96.4–96.8)	32,785	261	0.8 (0.7–0.9)
By gestational age (d)*						
49 or less	12,555	12,318	98.1 (97.9–98.3)	10,781	40	0.4 (0.3–0.5)
50–56	4,161	4,024	96.7 (96.1–97.2)	4,008	34	0.8 (0.6–1.2)
57–63	2,202	2,096	95.2 (94.2–96.0)	2,119	39	1.8 (1.3–2.5)
64–70	332	309	93.1 (89.6–95.5)	306	9	2.9 (1.4–5.7)

CI, confidence interval.

All outcomes are based on patients for whom outcome was determined (patients without follow-up are not included).

* Not all studies reported outcome within each specific gestational age range; outcomes are calculated using only those studies with outcome data presented by gestational age.

Table 2. Efficacy and Ongoing Pregnancy Rates With Mifepristone Followed in 24 Hours by Buccal Misoprostol for Medical Abortion Through 63 Days of Gestation

Study, Location	Study Design	Gestational Age (d)	Oral Mifepristone Dose (mg)	Buccal Misoprostol Dose (micrograms)
Raghavan, 2010, ²¹ Moldova*	Prospective	63 or less	200	400
Giri, 2011, ¹⁷ Nepal	Prospective	63 or less	200	800
Ngoc, 2011, ¹⁸ Vietnam	Prospective	63 or less	200	800
Blum, 2012, ¹⁹ Tunisia, Vietnam	Prospective	63 or less	200	800
Dahiya, 2012, ²⁰ India	Prospective	56 or less	200	800
Alam, 2013, ¹³ Bangladesh†	Prospective	63 or less	200	800
Total per category				

NR, not reported.

Data are n/N (%) unless otherwise specified.

All outcomes are based on patients for whom outcome was determined (patients without follow-up are not included).

* Five patients lost to follow-up in report without gestational age specified; all assumed to have gestational age 49 days or less for this review.

† Data were recalculated to present results only of those women who were pregnant at the time of receiving mifepristone and buccal misoprostol.

Table 3. Efficacy and Ongoing Pregnancy Rates With Mifepristone Followed in 24–48 Hours by Buccal Misoprostol for Medical Abortion Through 63 Days of Gestation

Study, Location	Study Design	Gestational Age (d)	Oral Mifepristone Dose (mg)	Buccal Misoprostol Dose (micrograms)	Time Interval Between Mifepristone and Misoprostol (h)
Middleton, 2005, ¹¹ U.S.	Prospective	56 or less	200	800	24–48
Winikoff, 2008, ²⁴ U.S.	Prospective	63 or less	200	800	24–36
Fjerstad, 2009, ²² U.S.*	Retrospective	59 or less	200	800	24–48
Boersma, 2011, ¹⁴ Curacao†	Prospective	63 or less	200	800	24–48
Grossman, 2011, ²⁵ U.S.	Prospective	63 or less	200	800	24–48
Chong, 2012, ³¹ Georgia, Vietnam	Prospective	63 or less	200	400	36–48
				800	36–48
Goldstone, 2012, ²⁶ Australia	Retrospective	63 or less	200	800	24–48
Ngo, 2012, ²⁷ China	Retrospective	63 or less	200	800	36–48
Winikoff, 2012, ¹⁵ U.S.‡	Prospective	57–63	200	800	24–48
Chai, 2013, ²³ Hong Kong§	Prospective	63 or less	200	800	48
Louie, 2014, ²⁸ Azerbaijan	Prospective	63 or less	200	800	24–48
Ngoc, 2014, ²⁹ Vietnam	Prospective	63 or less	200	800	24–48
Peña, 2014, ¹⁶ Mexico	Prospective	63 or less	200	800	24–48
Gatter, 2015, ³⁰ U.S.	Retrospective	63 or less	200	800	24–48
Total per category					

NR, not reported.

Data are n/N (%) unless otherwise specified.

All outcomes are based on patients for whom outcome was determined (patients without follow-up are not included).

* Results in publication presented in categories of 28 or less, 28–34, 35–41, 42–48, 49–55, and 56–59 days of gestation. Results for women with pregnancies through 59 days included in overall clinical outcome analysis and only data from 48 days or less of gestation included into gestational age-specific results; outcomes for pregnancies 48 days or less were recalculated based on the manuscript text and table.

† Results in publication presented in categories of 49 or less, 50–63, and 64–70 days of gestation. Results for women with pregnancies through 63 days included in overall clinical outcome analysis and only data from 49 days or less of gestation included into gestational age-specific results.

‡ Study included women with pregnancies 57–70 days of gestation; only results for women with pregnancies 57–63 days of gestation included.

§ Results in publication presented in categories of 49 or less and 50–63 days of gestation; only data from 49 days or less of gestation included into gestational age-specific results.



Successful Abortion				Ongoing Pregnancy			
Overall	49 d or Less	50–56 d	57–63 d	Overall	49 d or Less	50–56 d	57–63 d
264/272 (97.1)	226/234 (96.6)	27/27 (100)	11/11 (100)	4/272 (1.5)	4/234 (1.7)	0/27 (0.0)	0/11 (0.0)
89/95 (93.6)	NR	NR	NR	1/95 (1.1)	NR	NR	NR
194/201 (96.5)	158/162 (97.5)	25/28 (89.3)	11/11 (100)	3/201 (1.5)	1/162 (0.6)	2/28 (7.1)	0/11 (0.0)
195/210 (92.9)	105/109 (96.3)	64/74 (86.5)	26/27 (96.3)	3/210 (1.4)	1/109 (0.9)	2/74 (2.7)	0/27 (0.0)
46/50 (92.0)	NR	NR	NR	0/50 (0.0)	NR	NR	NR
545/587 (92.8)	NR	NR	NR	NR	NR	NR	NR
1,333/1,415 (94.2)	489/505 (96.8)	116/129 (89.9)	48/49 (98.0)	11/828 (1.3)	6/505 (1.2)	4/129 (3.1)	0/49 (0.0)

examining the efficacy of mifepristone followed by buccal misoprostol for medical abortion through 70 days of gestation using the search terms “mifepristone and medical abortion” and “buccal and miso-

prostol.” We used November 2005 as the earliest publication date limit because it is the known time of the first study reporting mifepristone followed by buccal misoprostol.¹¹ We also searched through

Successful Abortion, n/Total (%)				Ongoing Pregnancy, n/Total (%)			
Overall	49 d or Less	50–56 d	57–63 d	Overall	49 d or Less	50–56 d	57–63 d
205/216 (94.9)	NR	NR	NR	2/216 (0.9)	NR	NR	NR
405/421 (96.2)	207/213 (97.2)	89/93 (95.7)	109/115 (94.8)	4/421 (1.0)	2/213 (0.9)	0/93 (0.0)	2/115 (1.7)
1,326/1,349 (98.3)	946/961 (98.4)	NR	NR	6/1,349 (0.4)	NR	NR	NR
275/281 (97.9)	184/186 (98.9)	NR	NR	NR	NR	NR	NR
439/449 (97.8)	NR	NR	NR	4/449 (0.9)	NR	NR	NR
535/555 (96.4)	270/275 (98.2)	182/193 (94.3)	83/87 (95.4)	8/555 (1.4)	1/275 (0.4)	5/193 (2.6)	2/87 (2.3)
540/560 (96.4)	259/270 (95.9)	201/204 (98.5)	80/86 (93.0)	5/560 (0.9)	2/270 (0.7)	1/204 (0.5)	2/86 (2.3)
10,690/11,155 (96.5)	NR	NR	NR	83/11,155 (0.6)	NR	NR	NR
152/167 (91.0)	NR	NR	NR	NR	NR	NR	NR
304/325 (93.5)	NR	NR	304/325 (93.5)	10/325 (3.1)	NR	NR	10/325 (3.1)
43/45 (95.6)	22/22 (100)	NR	NR	0/45 (0.0)	0/22 (0.0)	NR	NR
840/863 (97.3)	608/627 (97.0)	152/153 (99.3)	80/83 (96.4)	7/863 (0.8)	NR	NR	NR
1,298/1,371 (94.7)	NR	NR	NR	36/1,371 (2.6)	NR	NR	NR
943/969 (97.3)	540/551 (98.0)	239/247 (96.8)	164/171 (95.9)	6/969 (0.6)	3/551 (0.6)	1/247 (0.4)	2/171 (1.2)
13,066/13,373 (97.7)	8,793/8,945 (98.3)	3,045/3,142 (96.9)	1,228/1,286 (95.5)	70/13,373 (0.5)	26/8,945 (0.3)	23/3,142 (0.7)	21/1,286 (1.6)
31,061/32,099 (96.8)	11,829/12,050 (98.2)	3,908/4,032 (96.9)	2,048/2,153 (95.1)	241/31,651 (0.8)	34/10,276 (0.3)	30/3,879 (0.8)	39/2,070 (1.9)



Table 4. Outcomes After a Repeat Dose of Misoprostol for Persistent Gestational Sac After Initial Treatment With Mifepristone and Buccal Misoprostol Through 63 Days of Gestation

Study, Country	Gestational Age (d)	Buccal Misoprostol Dose (micrograms)	Interval Between Mifepristone and Misoprostol (h)	Total No. of Patients	Eligible for 2nd Dose of Misoprostol	Chose to Have 2nd Dose of Misoprostol	Success After 2nd Dose of Misoprostol
Raghavan, 2010, ²¹ Moldova	63 or less	400	24	277	5 (1.8)	2 (40.0)	2 (100.0)
Winikoff, 2008, ²⁴ U.S.	63 or less	800	24–36	421	NR	14*	13 (92.9)
Winikoff, 2012, ¹⁵ U.S. [†]	57–63	800	24–48	325	17 (5.2)	13 (76.5)	10 (91.0)*
Louie, 2014, ²⁸ Azerbaijan	63 or less	800	24–48	863	28 (3.2)	16 (57.1)	16 (100.0)

NR, not reported.

Data are n (%) unless otherwise specified.

All patients received regimens with 200 mg mifepristone orally.

* Unable to calculate percent success because the number of women eligible for a second dose of misoprostol was not reported.

† Study included women with pregnancies through 70 days of gestation; only results for women with pregnancies through 63 days of gestation included.

* Only 11 participants waited 1 week for evaluation and were used in the study to calculate success.

the reference sections of all identified manuscripts for other relevant studies. Lastly, we reviewed ClinicalTrials.gov (www.clinicaltrials.gov) for any completed randomized clinical trials that used mifepristone and buccal misoprostol in their protocol for medical abortion.

STUDY SELECTION

Only manuscripts discussing use of mifepristone and buccal misoprostol for medical abortion through

10 weeks of gestation were eligible for inclusion. Studies were excluded if clinical outcomes were not reported. If more than one study was published with duplicate data, only the study with the larger data set was included.

Both authors independently extracted study information, including the first author, year of publication, country in which the study was performed, study design, gestational age of the study population, number of patients enrolled and with follow-up,

Table 5. Complication Rates After Medical Abortion Through 63 Days of Gestation With Mifepristone and Buccal Misoprostol as Compared With Mifepristone and Oral Misoprostol

Study, Country	Gestational Age (d)	Mifepristone Dose (mg)	Misoprostol Dose (micrograms), Route	Interval Between Mifepristone and Misoprostol (h)
Middleton, 2005, ¹¹ U.S.	56 or less	200	800, buccally	24–48
Winikoff, 2008, ²⁴ U.S.	63 or less	200	800, buccally	24–36
Goldstone, 2012, ²⁶ Australia	63 or less	200	800, buccally	24–48
Winikoff, 2012, ¹⁵ U.S. [‡]	63 or less	200	800, buccally	24–48
Gatter, 2015, ³⁰ U.S.	63 or less	200	800, buccally	24–48
Spitz, 1998, ² U.S.	63 or less	600	400, orally	48

ED, emergency department; NR, not reported.

Data are % unless otherwise specified.

All mifepristone administered orally.

* Reasons include medically necessary, incomplete abortion, persistent sac, and patient request.

† Four patients (1.9%) required intravenous fluids, but it was not specified if these patients were treated in the emergency department or required hospitalization.

‡ Study included women with pregnancies through 70 days of gestation; only results for women with pregnancies through 63 days of gestation are included.

§ Rate was 6.9% in a subset of 827 women through 49 days of gestation.



regimen used including repeat misoprostol dosing, and outcomes related to treatment efficacy, ongoing pregnancy rates, complications, and side effects.

Efficacy and ongoing pregnancy rates were abstracted as an overall rate and also categorized by gestational age in days in reference to completed weeks (eg, 49 days or less, 50–56 days, 57–63 days, 64–70 days). Efficacy is defined as complete expulsion of the pregnancy without need for surgical intervention. If study results were not presented in these categories, we recalculated, when possible, the gestational age-specific data based on tables and text within the manuscript. If we were unable to perform a reliable calculation, we excluded gestational age-specific data. Individual study outcomes were recalculated to exclude any patients who were not pregnant at the time of treatment. We then combined outcomes across studies to create summary statistics for efficacy and ongoing pregnancy as well as outcomes based on the interval between mifepristone and misoprostol administration.

Fisher's exact tests or χ^2 analyses were used to compare outcomes by gestational age, as appropriate. We considered a *P* value of .05 as statistically significant.

RESULTS

We identified 443 studies in the literature search and reviewed 28 full-text articles for eligibility. No additional studies were identified from searching the reference sections of the identified manuscripts or from clinicaltrials.gov. Eight records were excluded that had duplicate data (*n*=2), did not include buccal

misoprostol in the medical abortion regimen (*n*=3), and did not report efficacy and ongoing pregnancy outcomes (*n*=2). We also excluded one additional study that was a pilot trial evaluating simultaneous dosing of mifepristone and buccal misoprostol and found clinically unacceptable success rates.¹² The 20 manuscripts in this review include a dosing interval of at least 24 hours between mifepristone and buccal misoprostol for medical abortions through 70 days of gestation. We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting of study selection (Fig. 1).

Primary outcome definitions were similar across the included studies. All of the studies defined successful abortion as one in which the pregnancy was expelled from the uterus without need for surgical evacuation during the follow-up period for any reason. Ongoing pregnancy was defined in all studies as a viable gestation at follow-up ultrasound evaluation performed per study protocol or when clinically indicated except one study that defined a viable gestation as an increase in uterine size on follow-up examination consistent with an ongoing pregnancy.¹³

The overall efficacy and continuing pregnancy rate after mifepristone followed by buccal misoprostol is 96.6% and 0.8%, respectively, through 70 days of gestation in the 33,846 women who were included in this systematic review (Table 1). However, only 332 women are reported in the literature between 64 and 70 days of gestation from three trials^{14–16} with 304 of the patients from a single trial.¹⁴ The overall efficacy at 64–70 days of gestation is 93.1%. Ongoing pregnancy rate at 64–70 days of gestation (*n*=306) is 2.9%

Total No. of Patients	Surgical Evacuation for Reasons Other Than Continuing Pregnancy*	Blood Transfusion	ED Visits	Hospitalization Related to Medical Abortion	Infection
216	4.2	0.5	NR [†]	NR [†]	0.5
421	2.9	NR	2.9	NR	NR
13,345	2.9	0.08	NR	NR	0.2
325	3.4	0.6	3.7	0.9	0.3
13,373	1.8	0.03	NR	0.04	0.01
2,015	8.9 [§]	0.2	NR	1.3	0.9



Table 6. Reported Side-Effect Rates After Medical Abortion Through 63 Days of Gestation With Mifepristone and Buccal Misoprostol as Compared With Mifepristone and Oral Misoprostol

Study, Country	Gestational Age (d)	Mifepristone Dose (mg)	Misoprostol Dose (micrograms), Route	Interval Between Mifepristone and Misoprostol (h)
Middleton, 2005, ¹¹ U.S.	56 or less	200	800, buccally	24–48
Winikoff, 2008, ²⁴ U.S.	63 or less	200	800, buccally	24–36
Raghavan, 2010, ²¹ Moldova	63 or less	200	400, buccally	24
Ngoc, 2011, ¹⁸ Vietnam	63 or less	200	800, buccally	24
Chong, 2012, ³¹ Georgia, Vietnam	63 or less	200	400, buccally	36–48
			800, buccally	36–48
Winikoff, 2012, ¹⁵ U.S.*	63 or less	200	800, buccally	24–48
Blum, 2012, ¹⁹ Tunisia, Vietnam	63 or less	200	800 buccally	24
Dahiya, 2012, ²⁰ India	56 or less	200	800, buccally	24
Chai, 2013, ²³ Hong Kong	63 or less	200	800, buccally	48
Louie, 2014, ²⁸ Azerbaijan	63 or less	200	800, buccally	24–48
Pena, 2014, ¹⁶ Mexico	More than 64 [†]	200	800, buccally	24–48
Spitz, 1998, ² U.S.	49 or less	600	400, orally	48
	63 or less			

NR, not reported.

Data are % unless otherwise specified.

All mifepristone administered orally.

* Study included women with pregnancies through 70 days of gestation; only results for women with pregnancies through 63 days of gestation included.

[†] Two patients were greater than 64 days of gestation; actual gestational age not reported.

as compared with 1.8% at 57–63 days of gestation ($n=2,119$) ($P=.19$).

Six studies ($n=1,415$) examined clinical outcomes when women were instructed to use buccal misoprostol 24 hours after mifepristone (Table 2). Gestational age-specific outcomes were reported in the literature for 505, 129, and 49 women with pregnancies 49 days or less, 50–56 days, and 57–63 days of gestation, respectively. All studies used a regimen with 200 mg mifepristone and 800 micrograms misoprostol buccally^{13,17–20} except for one study that used 200 mg mifepristone and 400 micrograms misoprostol buccally.²¹ Clinical outcomes for one study, which included women who were treated but were actually not pregnant, were recalculated to include only women who were pregnant.¹³

An additional 14 studies ($n=32,099$) examined clinical outcomes when women were instructed to use buccal misoprostol between 24 and 48 hours after mifepristone (Table 3). Gestational age-specific data were excluded from three studies that did not report their results in the prespecified gestational age ranges.^{14,22,23} Outcomes by gestational age were reported for 12,050, 4,032, and 2,153 women with pregnancies 49 days or less, 50–56 days, and 57–63 days of gestation, respectively. All studies used 800 micrograms misoprostol buccally^{11,14–16,22–30} except for one study that reported clinical outcomes with 400

micrograms misoprostol buccally.³¹ One study described the actual time interval at which patients administered misoprostol after mifepristone, reporting a median interval of 48 hours (range 25–52 hours) for women who took mifepristone at home and a median interval of 47 hours (range 26–54 hours) for women that took mifepristone in the clinic.²⁸

Success rates through 63 days of gestation from studies reporting a 24-hour interval between mifepristone and misoprostol differ significantly from the rates in studies with a 24- to 48-hour interval overall (94.2% compared with 96.8%, respectively, $P<.001$), among gestations 49 days or less (96.8% compared with 98.2%, respectively, $P=.046$) and gestations 50–63 days (92.1% compared with 96.3%, respectively, $P=.009$). Two studies included intervals of 36–48 hours^{27,31} and one for 48 hours.²³ When these studies are excluded from the 24- to 48-hour group in the previous calculations, the results remain statistically significant for the overall (94.2% compared with 96.8%, respectively, $P<.001$), 49 days or less of gestation (96.8% compared with 98.2%, respectively, $P=.04$), and 50–63 days of gestation (92.1% compared with 96.3%, respectively, $P=.008$) calculations. The overall ongoing pregnancy rate through 63 days of gestation was not different among studies reporting a 24-hour or 24- to 48-hour interval between mifepristone and



Total No. of Patients	Nausea	Vomiting	Diarrhea	Weakness	Headache	Fever	Dizziness
216	69.4	37.0	36.1	54.6	43.5	42.1	40.7
414	75.1	47.6	43.0	58.0	41.1	47.6	39.4
266	54.1	22.2	NR	51.1	17.7	18.0	29.3
200	56.5	26.0	58.5	NR	NR	24.5	NR
555	44.0	16.0	NR	38.0	32.0	26.0	26.0
560	47.0	22.0	NR	42.0	33.0	33.0	24.0
318	50.0	35.8	17.9	NR	NR	11.9	NR
209	45.9	37.8	61.2	NR	NR	28.2	NR
50	64.0	16.0	8.0	NR	2.0	12.0	NR
45	46.7	20.0	31.1	NR	17.8	22.2	31.1
860	46.7	20.0	1.9	NR	NR	19.7	NR
969	34.0	26.0	60.0	21.0	14.0	45.0	13.0
859	61.5	25.8	20.3	NR	NR	NR	NR
1,851	67.3	33.9	22.9	NR	32.0	4.0	12.0

misoprostol (1.3% compared with 0.8%, respectively, $P=.10$).

Several studies using buccal misoprostol allowed the option of repeat misoprostol at follow-up 1 week after mifepristone for persistent gestational sac; however, few report specific outcomes. Table 4 highlights success rates after a repeat dose of misoprostol in reports that included these specific outcomes. In these study protocols, women with an ongoing pregnancy at follow-up were recommended to undergo uterine suction curettage, whereas women who had a nonviable pregnancy with a persistent gestational sac were given the options of expectant management, suction curettage, or a second dose of misoprostol. Overall, women who received a second dose of misoprostol experienced expulsion rates between 91.0% and 100.0%.

Adverse outcomes after medical abortion for selected studies are shown in Table 5. Rates of surgical evacuation for reasons other than ongoing pregnancy range from 1.8% to 4.2% in women who received mifepristone followed by buccal misoprostol, which is lower than the 6.9% surgical evacuation rate reported in women who received mifepristone followed by oral misoprostol through 49 days of gestation.² Blood transfusion and infection are uncommon, occurring in approximately 0.03–0.6% and 0.01–0.5% of patients, respectively. Adverse outcomes of emergency department visits (2.9–3.7%) and hospitalizations (0.04–0.9%) are inconsistently reported with variable rates across studies.

Reported treatment-associated side effects generally include nausea, vomiting, diarrhea, weakness, headache, dizziness, and thermoregulatory effects

such as fevers and chills. Table 6 includes the rates of reported side effects after mifepristone and buccal misoprostol compared with mifepristone and oral misoprostol. Nausea rates after buccal misoprostol are generally slightly lower compared with oral misoprostol, whereas diarrhea, fever, and dizziness rates are higher among women who received buccal misoprostol.

DISCUSSION

Over 30,000 women have now been included in studies examining mifepristone with buccal misoprostol for medical abortion since the first report using this regimen 10 years ago. These studies demonstrate that outpatient medical abortion regimens with mifepristone followed in 24–48 hours by buccal misoprostol are highly effective for pregnancy termination through 63 days of gestation. The complete abortion rate with this protocol is higher than the 92% rate with the FDA-approved regimen.² Furthermore, surgical evacuation for reasons other than continuing pregnancy is also lower with buccal compared with oral misoprostol regimens. Side-effect rates vary across studies, which may be related to different ways of defining these events or different patient populations. Overall, the side-effect profile of both regimens is comparable, and regimens with buccal misoprostol have been shown to be well tolerated and acceptable to participants.^{18,19,21,24}

Despite the presence of data supporting buccal misoprostol in medical abortion, there are still gaps in the literature, specifically with use 24 hours after mifepristone. Based on the available literature, the overall efficacy of regimens with a 24-hour interval

between mifepristone and buccal misoprostol is significantly lower than those with a 24- to 48-hour interval (94.2% compared with 98.1%). Our ability to fully understand if buccal misoprostol is more effective with a dosing interval closer to 48 hours is limited by the relatively small number of women in protocols with a 24-hour dosing as compared with a 24- to 48-hour dosing interval. Moreover, published trials only include outcomes by gestational age in 129 and 49 patients between 50–56 and 57–63 days of gestation, respectively. There is also a paucity of data on the actual time interval at which women actually administer misoprostol when instructed to use buccal misoprostol in a 24- to 48-hour window after mifepristone. Only one study reported the actual time elapsed between mifepristone and buccal misoprostol dosing; the median time interval was 47–48 hours.

Another obvious and important limitation of the available data is the relative lack of significant numbers of women who reported using mifepristone and buccal misoprostol beyond 63 days of gestation. Only 332 patients between 64 and 70 days of gestation are included in the literature, representing just 1.0% of the total number of women for which medical abortion outcomes with regimens containing buccal misoprostol are available. Based on current data, caution should be exercised when using buccal misoprostol in medical abortion regimens beyond 63 days in an outpatient setting until more evidence is available on efficacy rates and adverse effects.

Because regimens with mifepristone and buccal misoprostol are highly effective, large data sets are required to generate enough information to evaluate outcomes of a repeat misoprostol dose when abortion does not occur with initial treatment. These large data sets have been accumulated for regimens using vaginal misoprostol³²; however, little information is available in the published literature about repeat dosing of buccal misoprostol (Table 4). These limited data do support the potential efficacy of a repeat dose of buccal misoprostol. Because most women who choose medical abortion have a strong desire to avoid surgery, further medical treatment instead of vacuum aspiration may be preferable as long as further medical management is beneficial. Although these studies did not report expulsion rates after expectant management, most women with a persistent gestational sac but absent gestational cardiac activity would eventually expel the pregnancy.³³ Even so, a repeat dose of misoprostol may facilitate quicker expulsion and is a reasonable option for women.

This study informs clinicians about the evidence supporting the use of mifepristone and buccal misoprostol for medical abortion. To our knowledge, this systematic review includes all studies that utilize mifepristone and buccal misoprostol for early medical abortion. Of note, the evidence for these regimens is mainly derived from two large retrospective studies that contribute 76% of the data on clinical outcomes.^{26,30} To minimize heterogeneity of results, studies were grouped by the time interval between mifepristone and buccal misoprostol administration (ie, 24 hours and 24–48 hours) before analysis of overall efficacy and ongoing pregnancy rates. Further studies are needed to evaluate whether regimens with mifepristone followed in 24 hours by buccal misoprostol are effective, especially in pregnancies greater than 49 days of gestation. More evidence regarding clinical outcomes for pregnancies more than 63 days of gestation is needed before this practice becomes standard of care. With more high-quality data, women's health care providers can continue to provide the best evidence-based care to women.

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